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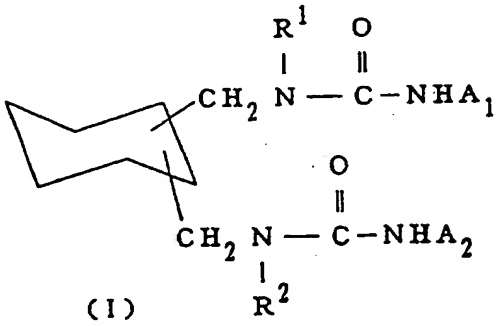
(54) CYCLOHEXANEDIUREA DERIVATIVE AND PROCESS FOR PRODUCING THE SAME

(57) The present invention provides a cyclohexanediurea derivative, inclusive of its salt, represented by the following formula (I):



(I)

wherein R^1 and R^2 are the same or different and they each represent a straight-chain or branched alkyl group having at least 3 carbons, a cycloalkyl group, a cycloalkyl group having a bridge head, a furyl group, a furyl lower alkyl group or an aralkyl group, A_1 and A_2 are the same or different and they each represent a phenyl, pyridyl, quinolyl, isoquinolyl or indolyl group which may have substituents; a process for production thereof; an intermediate thereof; pharmaceutical use, a method for treatment and use thereof.

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Description

TECHNICAL FIELD

The present invention relates to cyclohexanediurea derivatives which potently lower cholesterol and thus are useful as effective medicines for hyperlipidemia, atherosclerosis, etc.

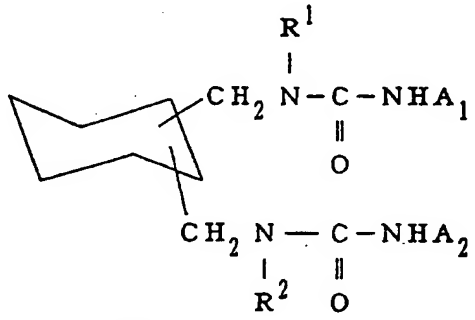
BACKGROUND ART

Lipometabolism disorders in hyperlipidemia, atherosclerosis, etc. are considered as a risk factor which closely relates to cerebral apoplexy, myocardial infarction, etc. Recent research has shown that cholesterol is esterified before its intestinal absorption and that esterification of cholesterol is also necessary for its accumulation on the endarterium or in the liver. It has been further elucidated that the enzyme which catalyzes the esterification of cholesterol is Acyl-CoA : cholesterol acyltransferase (hereinafter referred to as "ACAT"). Since the compounds inhibiting the activities of ACAT can inhibit the esterification of cholesterol, they are expected to prevent intestinal absorption of cholesterol or cholesterol accumulation on the endarterium and considered as very potential medicines for hyperlipidemia and atherosclerosis and various diseases caused by them. Conventional ACAT enzyme inhibitors can be classified based on the chemical structure into three groups: amido derivatives (Japanese Unexamined Patent Publications Nos. 23848/1988 and 278038/1990), urea derivatives (Japanese Unexamined Patent Publications Nos. 6455/1990, 294256/1991 and 220168/1991) and diurea derivatives (Japanese Unexamined Patent Publications Nos. 203360/1989 and 117651/1990). There has been no report of the diurea compound in which urea groups are linked to a cyclohexane ring through alkylene chains, which is the chemical structure according to the present invention.

In search of a new ACAT enzyme inhibitor more powerful than those of the prior art and effective as a medicine for hyperlipidemia, atherosclerosis, etc., the inventors of the present invention studied 1,2-, 1,3- and 1,4-positions on the cyclohexane ring and cis- or trans-isomers of diurea compounds in these positions and finally found that some isomers of cyclohexanediurea derivatives in specific positions are the compounds which fulfill the above-mentioned requirements. The present invention has been accomplished based on this finding.

DISCLOSURE OF THE INVENTION

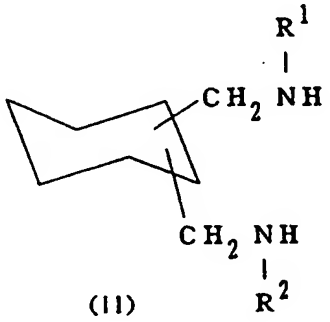
The present invention provides a cyclohexanediurea derivative represented by the following formula (I):



(I)

wherein R^1 and R^2 are the same or different and they each represent a straight-chain or branched alkyl group having at least 3 carbons, a cycloalkyl group, a cycloalkyl group having a bridge head, a furyl group, a furyl lower alkyl or an aralkyl group and A_1 and A_2 are the same or different and they each represent a phenyl, pyridyl, quinolyl, isoquinolyl or indolyl group which may have substituent(s); or a salt thereof.

The present invention also provides a cyclohexanediamine derivative represented by the following formula (II):



(II)

wherein R^1 and R^2 are as defined above; or a salt thereof.

The present invention further provides an ACAT enzyme inhibitor which comprises an effective amount of the cyclohexanediurea derivative of formula (I) or its salt and a pharmaceutically acceptable carrier.

The present invention also provides a medicine for hyperlipidemia which comprises an effective amount of the cyclohexanediurea derivative of formula (I) or its salt and a pharmaceutically acceptable carrier.

The present invention further provides a medicine for atherosclerosis which comprises an effective amount of the cyclohexanediurea derivative of formula (I) or its salt and a pharmaceutically acceptable carrier.

Furthermore, the present invention provides a method for inhibiting an ACAT enzyme which comprises administering an effective amount of the cyclohexanediurea derivative of formula (I) or its salt to a patient.

The present invention also provides a method for treating hyperlipidemia which comprises administering an effective amount of the cyclohexanediurea derivative of formula (I) or its salt to a patient.

The present invention also provides a method for treating atherosclerosis which comprises administering an effective amount of the cyclohexanediurea derivative of formula (I) or its salt to a patient.

Furthermore, the present invention provides use of the cyclohexanediurea derivative of formula (I) or its salt in inhibition of ACAT enzyme.

The present invention also provides use of the cyclohexanediurea derivative of formula (I) or its salt in treatment of hyperlipidemia.

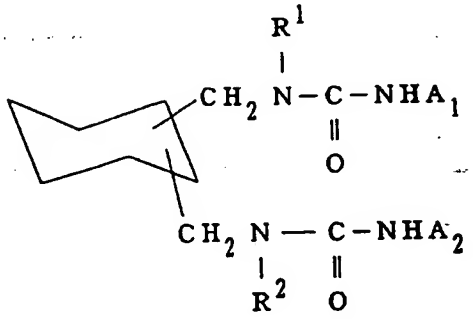
The present invention further provides use of the cyclohexanediurea derivative of formula (I) or its salt in treatment of atherosclerosis.

Furthermore, the present invention provides use of the cyclohexanediurea derivative of formula (I) or its salt in preparation of an ACAT enzyme inhibitor.

The present invention also provides use of the cyclohexanediurea derivative of formula (I) or its salt in preparation of a medicine for hyperlipidemia.

The present invention also provides use of the cyclohexanediurea derivative of formula (I) or its salt in preparation of a medicine for atherosclerosis.

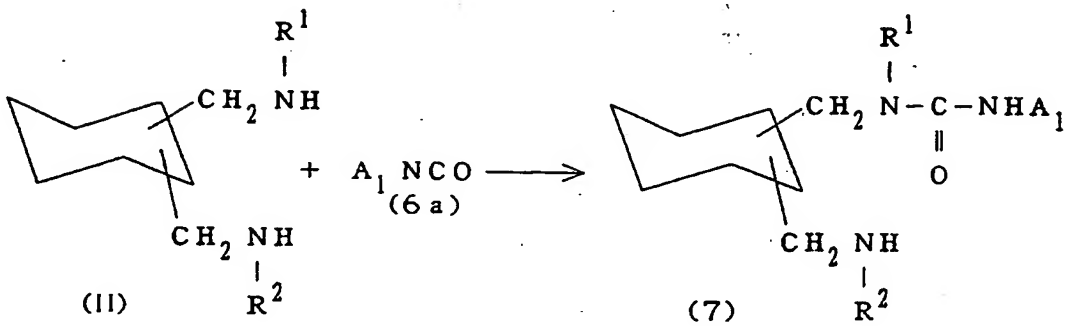
The present invention also provides a process for preparing the cyclohexanediurea derivative of formula (I):



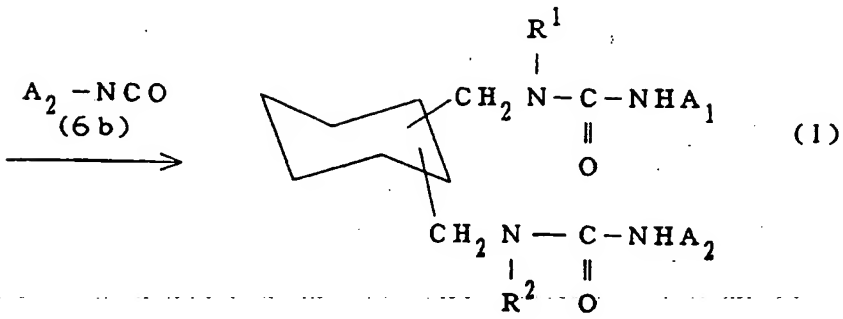
(I)

wherein R^1, R^2, A_1 and A_2 are as defined above, in accordance with one of the following (Process A) to (Process D):

(Process A)



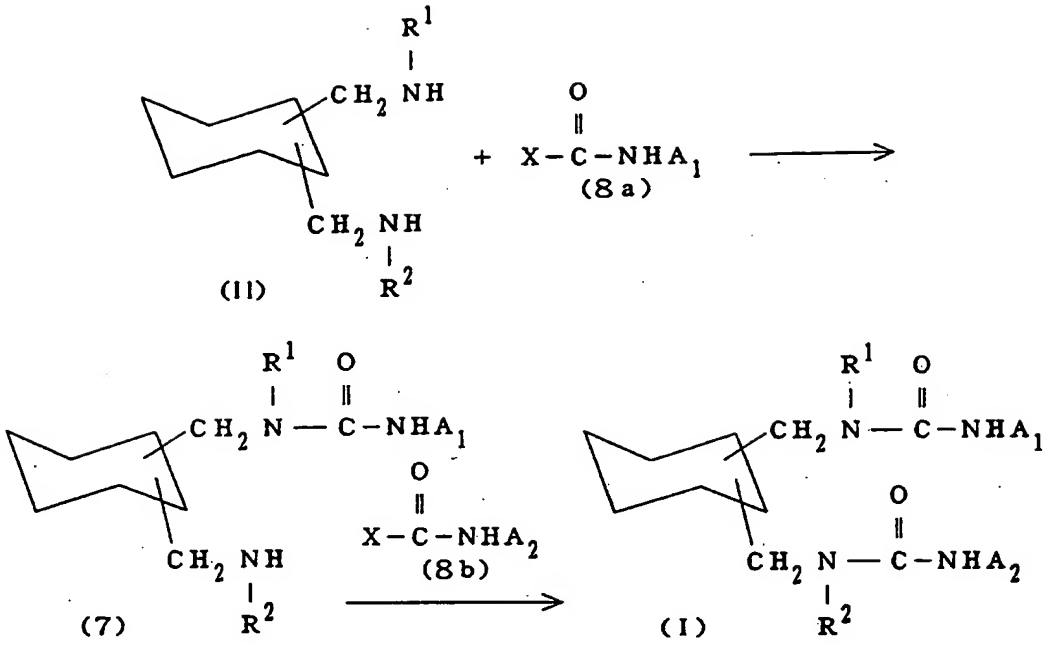
(II) (6a) (7)



(6b) (I)

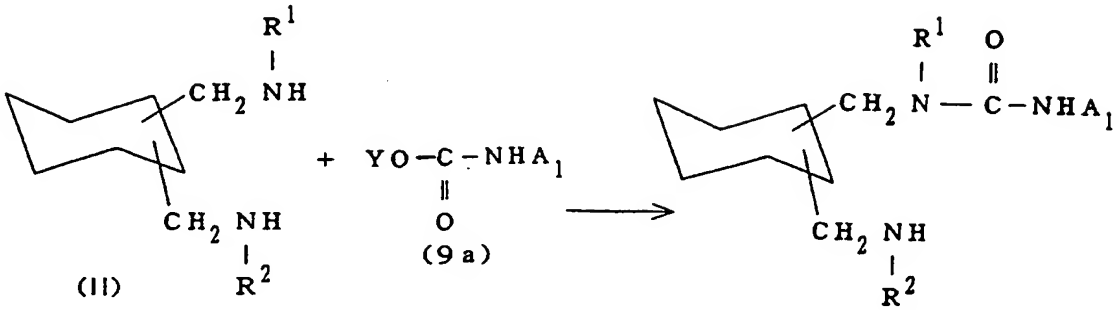
wherein R^1, R^2, A_1 and A_2 are as defined above,

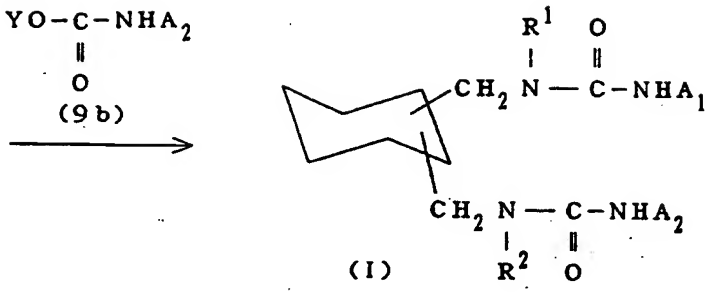
(Process B)



wherein R^1, R^2, A_1 and A_2 are as defined above,

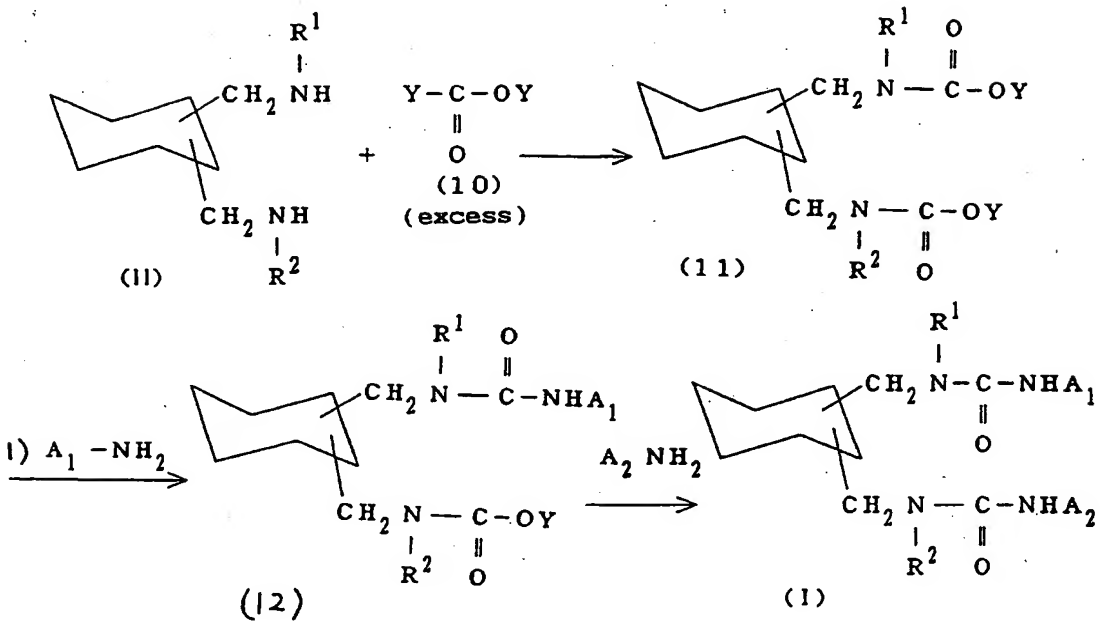
(Process C)





wherein R^1, R^2, A_1 and A_2 are as defined above, and

(Process D)



wherein R^1, R^2, A_1 and A_2 are as defined above.

The cyclohexanediurea derivative (II) is a synthetic intermediate for preparation of the cyclohexanediurea derivative of formula (I) or its salt.

The present invention will be described below in detail. The compound (I) of the invention has such a structure that two urea derivatives are linked to a cyclohexane ring through methylene chains, and includes a trans-1,2, cis-1,2, trans-1,3, cis-1,3, trans-1,4 or cis-1,4 cyclohexanediurea derivative, which varies depending on how the urea derivatives are linked. The compound (I) of the present invention preferably has trans-1,4, cis-1,4, or cis-1,3 bond. The cyclohexane ring may be chair or boat form.

In the definition of the formula (I), "the straight-chain or branched alkyl group having at least 3 carbon atoms" includes a C_{3-10} straight-chain or branched alkyl group, such as propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, heptyl, 1-methylheptyl, 1-methylhexyl, 2-

methylhexyl, 1-ethylpentyl, 1,1-dimetylpentyl, 1,2-dimethylpentyl, octyl, 1,5-dimethylhexyl, tert-octyl, nonyl, decyl and so on.

"The cycloalkyl group" includes a C_{3-10} cycloalkyl group which may have a C_{1-4} lower alkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-methylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 4-ethylcyclohexyl, 4-propylcyclohexyl, 4-butylcyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and so on.

"The cycloalkyl group which has a bridge head" includes adamantyl, norbornyl and so on.

"The furyl group" includes 2-furyl, 3-furyl and so on.

"The furyl lower alkyl group" includes furylmethyl, furylethyl, furylpropyl, furylisopropyl, furylbutyl, furylisobutyl, furyl sec-butyl, furyl tert-butyl, furylpentyl, furylisopentyl, furyl tert-pentyl, furylneopentyl and so on.

The substituent of "the phenyl, pyridyl, isoquinolyl, quinolyl or indolyl group which may have substituent(s)" includes a C_{1-5} lower alkyl group, a cyclic amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group having the same or different alkyl groups, a hydroxyl group, a lower alkoxy group, a lower alkoxycarbonyl group, a lower alkoxycarbonyloxy group, a cyano group, a nitro group, a halogen atom, a lower alkylcarbonyloxy group, a trihalogenomethyl group, and an acylamino group.

Among the substituents, the C_{1-5} lower alkyl group includes a straight-chain or branched alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and neopentyl. The cyclic amino group includes pyrrolidino, piperidino, morpholino, piperazino, homopiperazino and so on. The mono(lower)alkylamino group and the di(lower)alkylamino group having the same or different alkyl groups include an amino group substituted by one or two C_{1-5} lower alkyl groups mentioned above. The lower alkoxy group includes a C_{1-5} alkoxy group such as methoxy, ethoxy, propoxy, isopropyl, butoxy, sec-butoxy, tert-butoxy, pentoxy, sec-pentoxy, tert-pentoxy and so on. The lower alkoxycarbonyl group includes a C_{2-6} alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, sec-pentoxycarbonyl, tert-pentoxycarbonyl and so on. The lower alkoxycarbonyloxy group includes methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, sec-butoxycarbonyloxy, tert-butoxycarbonyloxy, pentoxycarbonyloxy, sec-pentoxycarbonyloxy, tert-pentoxycarbonyloxy and so on. The halogen atom includes fluorine, chlorine, bromine and iodine. The lower alkylcarbonyloxy group includes a C_{2-6} alkylcarbonyloxy group such as methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, sec-butylcarbonyloxy, tert-butylcarbonyloxy, pentylcarbonyloxy, sec-pentylcarbonyloxy, tert-pentylcarbonyloxy and so on. The trihalogenomethyl group includes trifluoromethyl, trichloromethyl and so on. The acylamino group includes a C_{2-5} acylamino group such as acetylamino, propionylamino, isopropionylamino, butyrylamino, isobutyrylamino, valerylamino, isovalerylamino, pivaloylamino and so on.

The phenyl, pyridyl, quinolyl, isoquinolyl or indolyl group represented by A may have one or more substituents mentioned above. Examples of such phenyl groups are 3-dimethylaminophenyl, 4-dimethylaminophenyl, 4-ethylmethylaminophenyl, 4-dietylaminophenyl, and 4-piperidinophenyl.

The said phenyl (2-6 positions), pyridyl (2-6 positions), quinolyl (2-8 positions), isoquinolyl (1, 3-8 positions) or indolyl (2-7 positions) may be linked to the amino group of urea in any of these positions.

Preferred species of the compound of formula (I) are as follows:

I. a cyclohexanediurea derivative of formula (I) wherein the urea derivatives are linked to the cyclohexane ring by trans-1,4, cis-1,4 or cis-1,3 bond, and R^1 or R^2 represents a cycloalkyl group or a branched alkyl group; and A_1 or A_2 represents 4-dimethylaminophenyl, 4-pyrrolidinophenyl or 4-piperidinophenyl; or a salt thereof;

II. a cyclohexanediurea derivative of formula (I) wherein $R^1 = R^2$ and $A_1 = A_2$; or a salt thereof;

III. a cyclohexanediurea derivative of formula (I) wherein R^1 and R^2 are the same or different and they each represent cyclopentyl, cyclohexyl, cycloheptyl or 4-methylcyclohexyl; or a salt thereof;

IV. a cyclohexanediurea derivative of formula (I) wherein A_1 and A_2 are the same or different and they each represent 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-pyrrolidinophenyl, 4-piperidinophenyl or 4-morpholinophenyl; or a salt thereof; and

V. a cyclohexanediurea derivative or salt thereof which is one of the compounds or salts given below in (1)-(10):

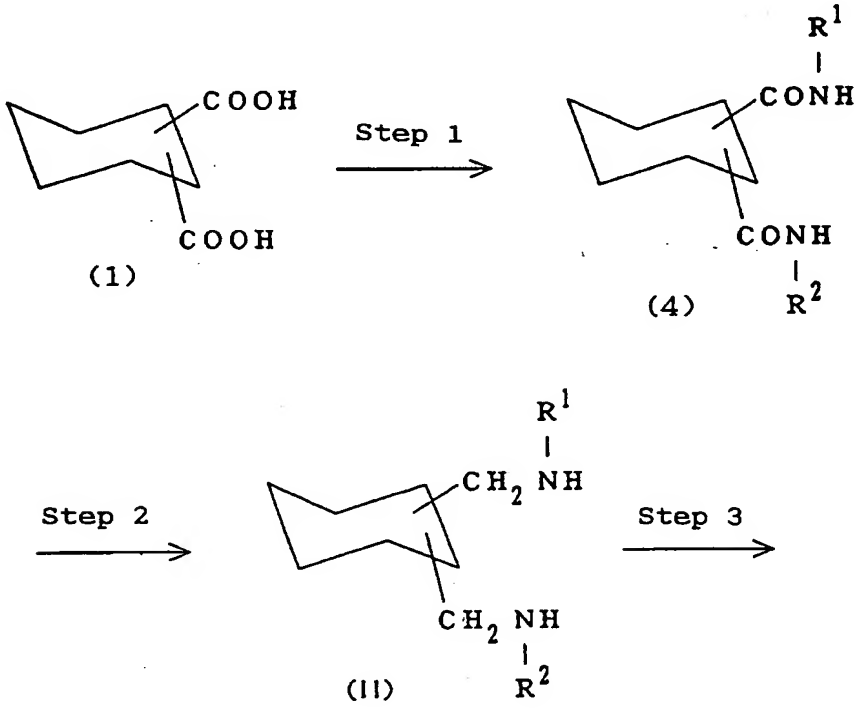
(1) a trans-1,4-bis[[1-cyclopentyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(2) a trans-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(3) a trans-1,4-bis[[1-cyclohexyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(4) a trans-1,4-bis[[1-cyclohexyl-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane or a salt thereof;
(5) a trans-1,4-bis[[1-cyclohexyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane or a salt thereof;
(6) a trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-(4-methylcyclohexyl)ureido]methyl]cyclohexane or a salt thereof;
(7) a trans-1,4-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(8) a trans-1,4-bis[[1-cycloheptyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(9) a trans-1,4-bis[[1-cycloheptyl-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane or a salt thereof; and

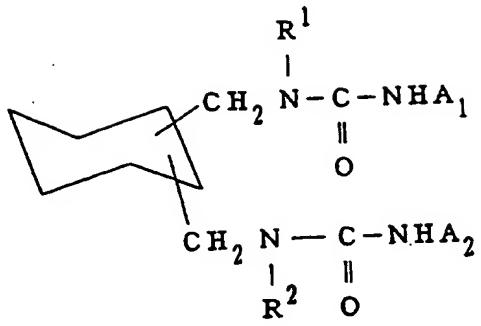
(10) a trans-1,4-bis[[1-cycloheptyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane or a salt thereof.

The compounds of formula (I) can also be formed into salts. Acid addition salts of the compound (I) are included in the present invention. The acid used to form such salts includes mineral acids and organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, citric acid, succinic acid, oxalic acid, fumaric acid, maleic acid, malic acid, tartaric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and so on. The salts can be produced by reacting these acids with the compound of formula (I) by conventional methods.

The compound of the invention can be prepared by various methods and there is no specific limitation on the method. The compound can be prepared, for example, by the following (Reaction scheme A).

(Reaction scheme A).



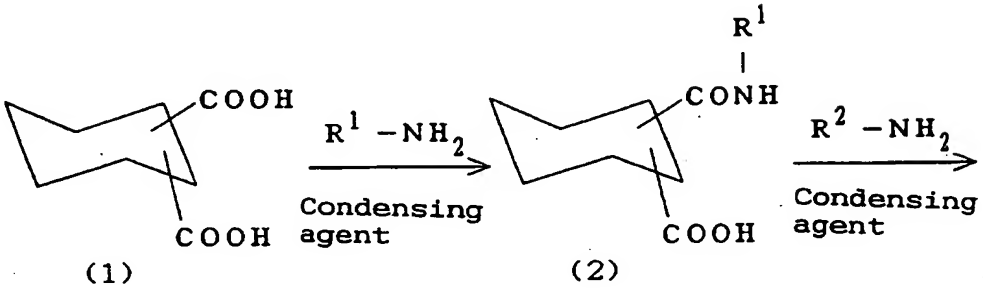


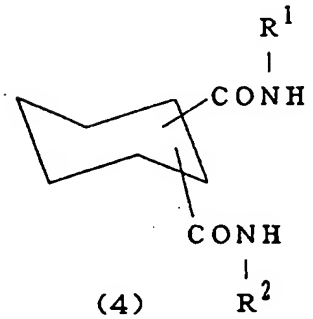
(1)

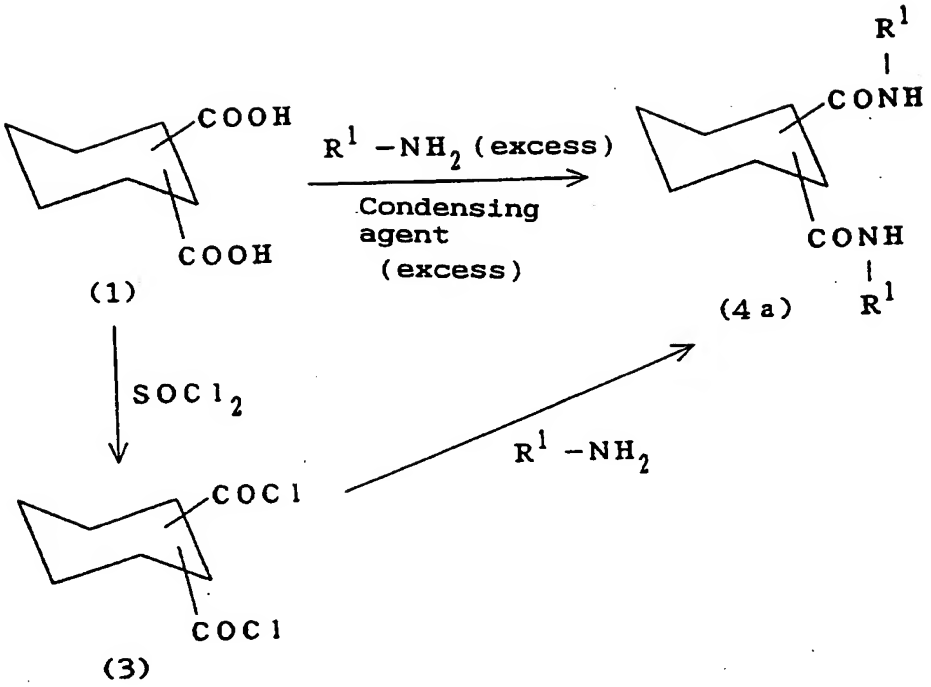
wherein R^1, R^2, A_1 and A_2 are as defined above.

(Step 1) to (Step 3) are described below.

(Step 1)







wherein R^1 and R^2 are as defined above.

The cyclohexanedicarbonic acid of formula (1) (which is a cis or trans, 1,2-, 1,3-, or 1,4-isomer) is reacted with a primary amine derivative represented by R^1NH_2 in the presence of a condensing agent to give a monoamide (2). The monoamide (2) is reacted with a primary amine derivative represented by R^2NH_2 in the presence of a condensing agent to give a diamide of formula (4).

The reaction between cyclohexanedicarbonic acid and R^1NH_2 is carried out using about 0.9-1.1 moles of R^1NH_2 and about 1.0-1.1 moles of a condensing agent per mole of cyclohexanedicarbonic acid in a solvent under cooling or at room temperature for about 1-5 hours. Examples of useful solvents are benzene, toluene, tetrahydrofuran (THF), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), etc. Examples of useful condensing agents are N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride acid salt (WSCD • HCl), carbonyldiimidazole, etc. A reaction promoter such as triethylamine, 1-hydroxybenzotriazole (HOBt) and N-hydroxysuccinimido can also be added in the reaction. The reaction mixture containing the starting dicarbonic acid, object monoamide (2) and diamide is subjected to separation and purification by a conventional method such as recrystallization, column chromatography or extraction with a solvent, thus giving an object monoamide (2).

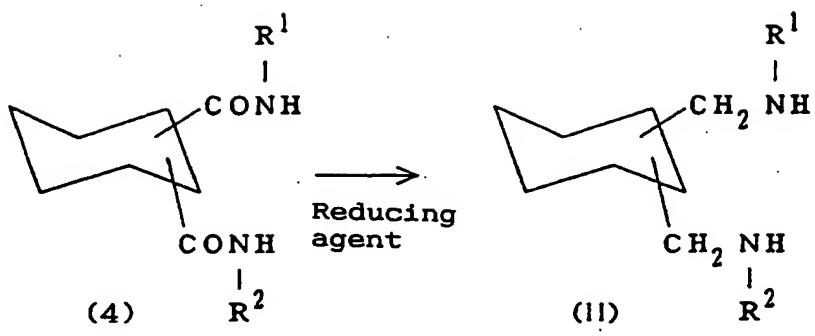
The monoamide (2) is then reacted with R^2NH_2 in the presence of a condensing agent under the same conditions as mentioned above, thus giving a diamide (4).

The diamide (4) wherein $R^1=R^2$ can be prepared by reacting cyclohexanecarbonic acid with an excess (at least 2 equivalents) of R^1NH_2 and a condensing agent in the same manner as mentioned above.

The diamide (4a) wherein $R^1=R^2$ can also be prepared by reacting cyclohexanedicarbonic acid (1) with a chlorizing agent such as thionylchloride and oxazalylchloride under cooling or at room temperature in the absence of a solvent or in a solvent inert to the reaction, such as benzene, toluene, hexane, dichloromethane and chloroform, thus converting cyclohexanedicarbonic acid into an acid chloride derivative of formula (3) and then allowing the derivative to react in an inert solvent such as benzene, toluene, hexane, dichloromethane, chloroform, THF, DMF and DMSO under ice-cooling or at room temperature, optionally using an inorganic base such as sodium carbonate, potassium carbonate and sodium hydrogencarbonate or an organic base such as triethylamine and pyridine to promote the reaction. The amine derivative represented by R^1NH_2 is usually used in an amount of 2 moles to an excess mole per mole of dicarbonic acid.

The diamide (4a) wherein $R^1=R^2$ can also be obtained by using at least 2 equivalents of an amine represented by R^1NH_2 and an condensing agent relative to the dicarbonic acid (1).

(Step 2)



(4) (II)

wherein R^1 and R^2 are as defined above.

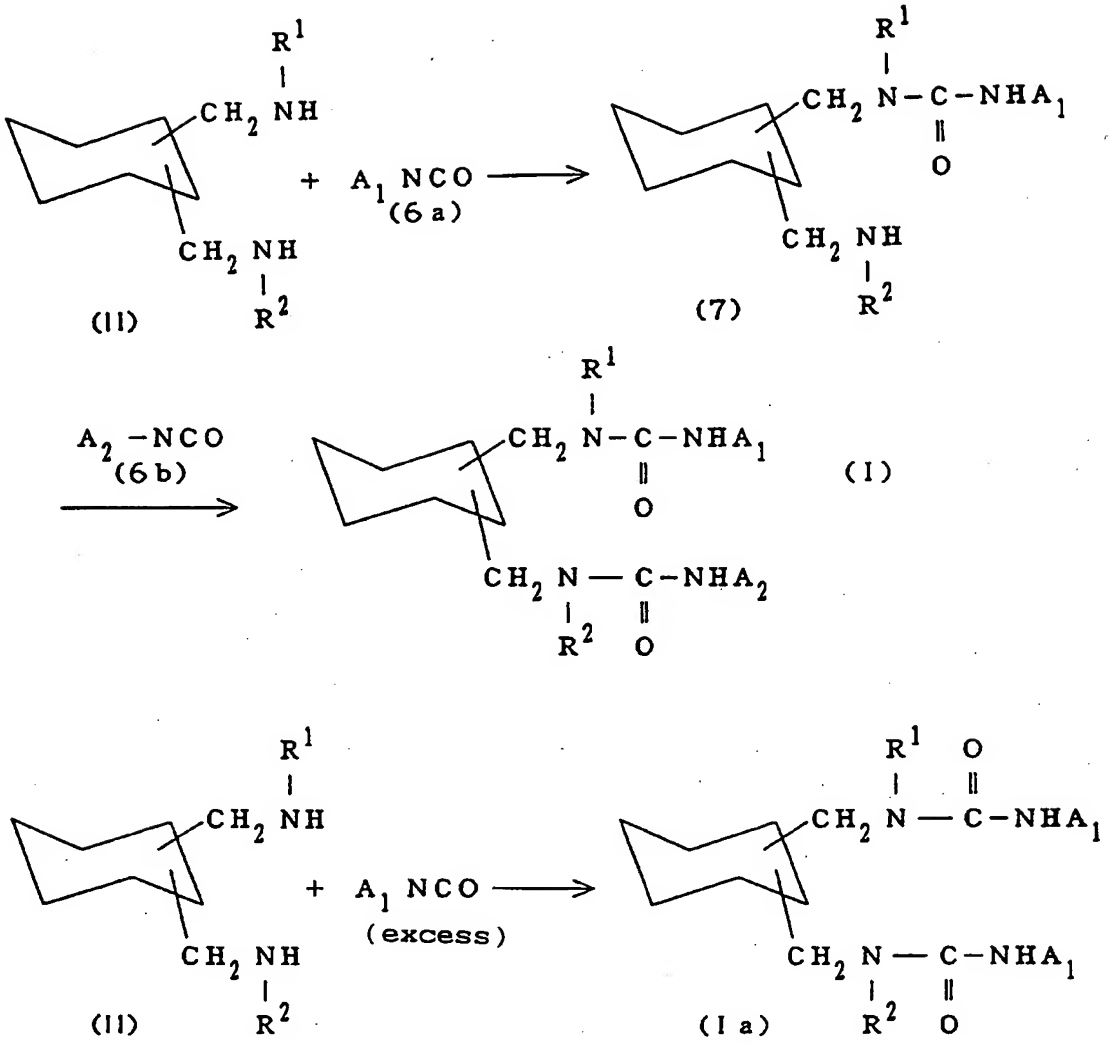
Step 2 is a reduction reaction of carbonyl groups of the diamide derivative of formula (4). In step 2, a diamide derivative of formula (4) is reacted in a solvent in the presence of a reducing agent, thus giving a reductant (II). The reaction is carried out using an equimolar to excess amount of the reducing agent relative to the diamide (4) at room temperature to about 100°C for about 2-24 hours.

Examples of useful solvents in the reduction reaction include solvents inert to the reaction, such as benzene, toluene, dioxane, THF, ether, and the like, among which THF is preferred. Examples of useful reducing agents include lithiumaluminum hydride (LAH), diisobutylaluminum hydride, sodium dihydro-bis(2-methoxyethoxy)aluminate, diborane, borantetrahydrofuran complex, borane dimethyl sulfide complex, and so on.

(Step 3)

The compound (I) according to the present invention can be produced by various methods. Some typical methods are shown below.

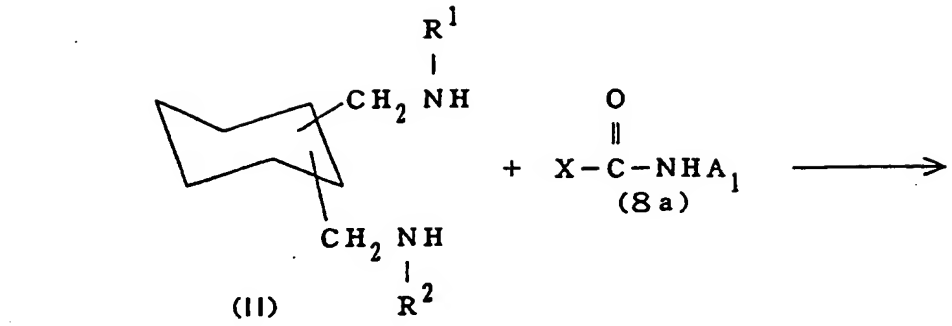
(Process 3-Ia)

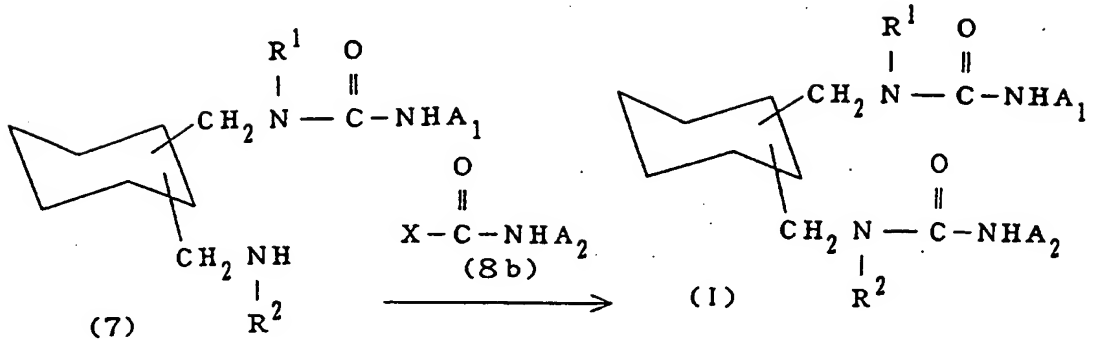


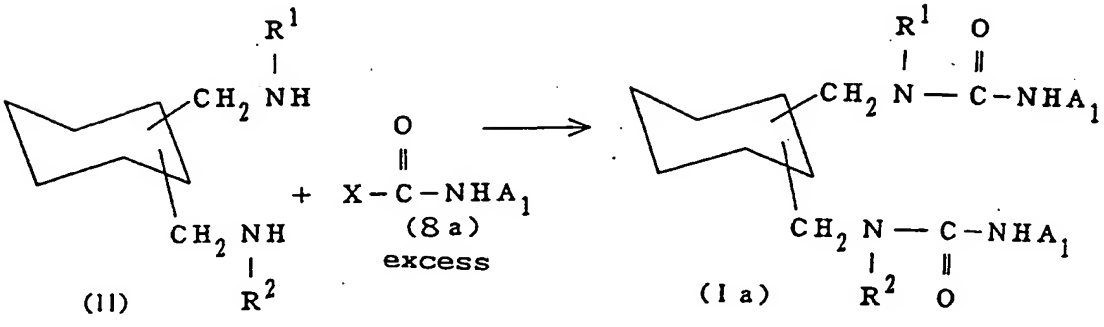
wherein R^1, R^2, A_1 and A_2 are as defined above.

The amine derivative of formula (II) is reacted with an isocyanate (6a) represented by A_1NCO in a solvent at room temperature to approximately the boiling point of the solvent for 3-72 hours, thus giving a monourea (7). The monourea (7) is reacted with an isocyanate (6b) to provide an object compound (I). Examples of useful solvents are pyridine, benzene, toluene, dioxane, THF, ether, dichloromethane, chloroform, n-hexane, acetonitrile, DMF, etc. The isocyanate (6a) is used in an amount of 0.9-1.1 equivalents per mole of the diamine of formula (II). After completion of the reaction, the monourea (7) is separated and purified by a conventional purification method such as extraction with a solvent, recrystallization and column chromatography. The diurea of formula (I) can be prepared by reacting the monourea (7) with an isocyanate (6b) under the same conditions as mentioned above. The diurea of formula (Ia) wherein $A_1=A_2$ is usually prepared using 2 moles to an excess of an isocyanate (6a) per mole of the amine derivative (II).

(Process 3-Ib)





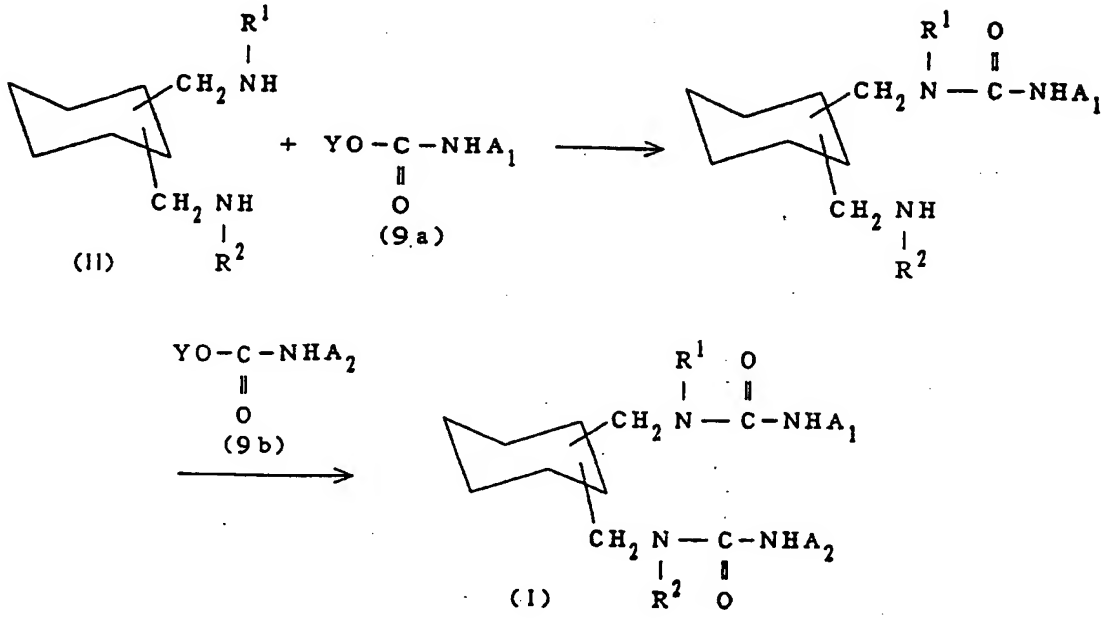


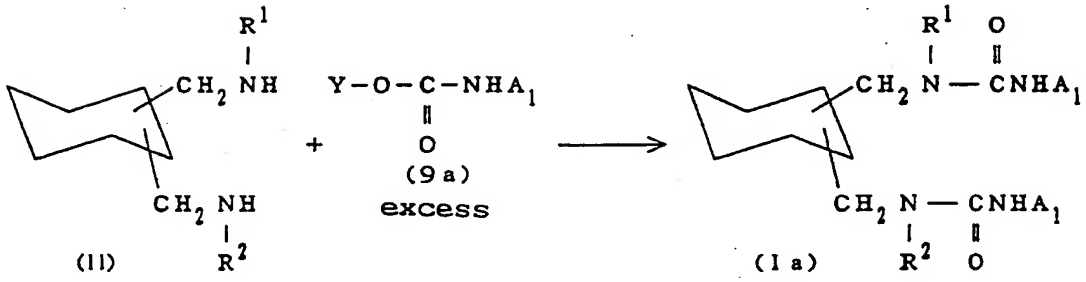
wherein X is a chlorine, bromine or iodine atom and R^1, R^2, A_1 and A_2 are as defined above.

One mole of an amine derivative of formula (II) is reacted with 1.0-1.1 moles of carbonyl halide (8a) in a solvent under ice-cooling or at room temperature for 1-6 hours to give a monourea (7). Examples of useful solvents are those inert to the reaction, such as benzene, toluene, dioxane, THF, ether, dichloromethane and chloroform. In the reaction, a base such as triethylamine, pyridine and dimethylaminopyridine can also be added in an amount of about 1.0-1.5 moles. After completion of the reaction, the reaction mixture is subjected to separation and purification in the same manner as in the above process 3-Ia, thus giving a monourea (7). The monourea (7) is reacted with carbonyl halide (8b) under the same conditions as mentioned above to give an object compound of formula (I).

The compound (Ia) wherein A_1=A_2 can be prepared by reacting an amine derivative of formula (II) with 2 equivalents to an excess of carbonyl halide (8a).

(Process 3-Ic)





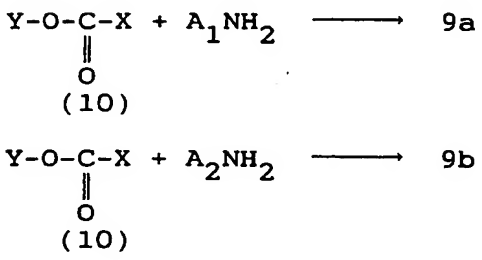
wherein Y represents a C_{1-5} lower alkyl group or a phenyl group, and R^1, R^2, A_1 and A_2 are as defined above.

One mole of an amine derivative of formula (II) is reacted with about 0.9-1.1 moles of a carbamic acid ester of formula (9a) in the presence of a solvent at about 0°C to approximately the boiling point of the solvent for 5-24 hours to give a monoamide (7). The monoamide (7) is separated and purified by a conventional purification method such as solvent extraction, column chromatography and recrystallization. The monoamide (7) is reacted with a carbamic acid ester of formula (9b) under the same conditions as mentioned above, thus giving an object compound of formula (I).

Examples of useful solvents are inert solvents such as benzene, toluene, dioxane, ether, THF, DMF, acetonitrile, chloroform, dichloromethane.

The compound (Ia) wherein A_1=A_2 according to the invention can be prepared by reacting an amine derivative of formula (II) with 2 equivalents to an excess of a carbamic acid ester (9a).

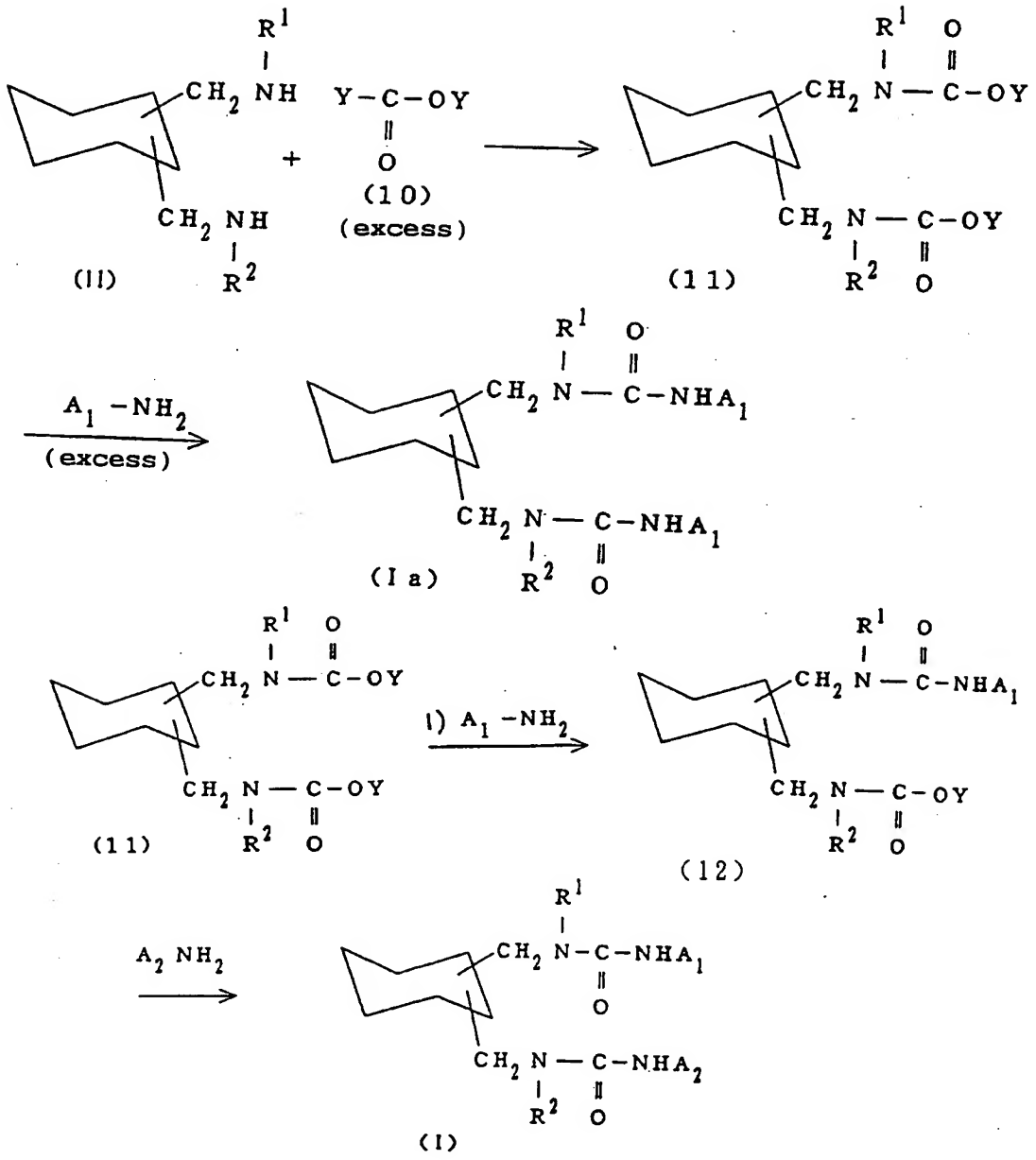
The carbamic acid ester used as the starting compound in the above reaction can be prepared by the following reaction:



wherein Y, X, A_1 and A_2 are as defined above.

The carbamic acid ester (9a) or (9b) can be prepared by reacting a carbonic acid halide (10) such as isobutylcarbonic acid chloride, methylcarbonic acid chloride and phenylcarbonic acid chloride with A_1NH_2 or A_2NH_2 in a solvent in the presence or absence of a base. Examples of useful solvents are inert solvents, such as benzene, toluene, dioxane, ether, THF, chloroform, and dichloromethane. Examples of useful bases are potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, sodium hydroxide, triethylamine, and N,N-dimethylaniline. The reaction is carried out under cooling or at room temperature for about 1-5 hours.

(Process 3-Id)



wherein Y, R^1, R^2, A_1 and A_2 are as defined above.

One mole of an diamine derivative of formula (II) is reacted with 2 equivalents to an excess of a carbonic acid halide (10) in a solvent under ice-cooling or at room temperature for 1-5 hours to give a dicarbamic acid ester (11). One mole of the ester (11) is reacted with 2 moles to an excess of A_1NH_2 at room temperature to approximately the melting point of the solvent for 2-12 hours to give a compound of formula (Ia).

Examples of useful solvents are inert solvents such as benzene, toluene, dioxane, ether, THF, chloroform and dichloromethane. The reaction between the diamine derivative of formula (II) and the carbonic acid halide (10) is carried out

advantageously in the presence of a base such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, sodium hydroxide, triethylamine and N,N-dimetylaniline.

The substitution reaction can be promoted by means of a phase transfer catalyst such as benzyltriethylammonium chloride, benzyltriethylammonium bromide, tetra-n-butylammonium chloride, tetra-n-butylammonium bromide, and tetra-n-butylammonium hydrogensulfate. The compound of formula (I) can also be prepared by reacting 1 mole of an ester (11) with 1 mole of A_1NH_2 and reacting the resulting monourea (12) with 1 mole or an excess of A_1NH_2 under the same conditions as mentioned above.

The isolation and purification can be done by a conventional chemical operation, such as extraction, recrystallization and various chromatographies.

The compound (I) of the present invention or a pharmacologically acceptable salt can be provided in a variety of dosage forms of preventive or therapeutic medicine. Examples of such forms are compositions for oral administration, injections, suppositories, attaching agents such as cataplasms and taping agents, ointments, creams and lotions. These dosage forms can be manufactured by conventional methods for preparing pharmaceutical compositions.

Solid pharmaceutical compositions for oral administration can be manufactured by optionally adding a binder, a disintegrator, a lubricant, a coloring agent, a flavor, a perfume, etc. to the compound of the invention and preparing the composition in the form of tablets, coated tablets, granule, powder, capsules, etc. by conventional methods. Conventional additives in this field can be used as such additives. Examples of useful excipients are lactose, sucrose, sodium chloride, glucose, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid. Examples of useful binders are water, ethanol, propanol, simple syrup, glucose syrup, starch solution, gelatin solution, carboxymethylcellulose, carboxypropylcellulose, hydroxypropylstarch, methylcellulose, ethylcellulose, shellac, calcium phosphate, and polyvinylpyrrolidone. Examples of useful disintegrators are dry starch, sodium alginate, agar powder, sodium hydrogen carbonate, calcium carbonate, sodium lauryl sulfate, stearyl monoglyceride, and lactose. Examples of useful lubricants are purified talc, salts of stearic acid, boric acid powder, and polyethylene glycol. Examples of useful flavors are sucrose, bitter orange peel, citric acid, and tartaric acid.

Liquid pharmaceutical compositions for oral administration can be manufactured by optionally adding a flavor, a buffer, a stabilizer, a perfume, etc. to the compound of the invention and preparing the composition in the form of internal medicine, syrup, elixir, etc. by conventional methods. Examples of useful flavors are the same as mentioned above. Examples of useful buffers include sodium citrate. Examples of useful stabilizers include tragacanth, gum arabic, and gelatin.

Injections can be manufactured by optionally adding a pH adjusting agent, a buffer, a stabilizer, an isotonic agent, a local anesthetic, etc. to the compound of the invention and preparing hypodermic, intramuscular or intravenous injections by conventional methods. Examples of useful pH adjusting agents and buffers are sodium citrate, sodium acetate, sodium phosphate, etc. Examples of useful stabilizers are sodium pyrosulfite, EDTA, thioglycollic acid, thiolactic acid, etc. Examples of useful local anesthetics are procaine hydrochloride, lidocaine hydrochloride, etc.

Suppositories can be manufactured by adding a known pharmaceutically acceptable carrier such as polyethylene glycol, lanolin, cacao butter and fatty acid triglyceride and optionally a surfactant such as Tween (trademark) to the compound of the invention and preparing suppositories by conventional methods.

Ointments can be manufactured by optionally adding a base, a stabilizer, a humectant, a preservative, etc. to the compound of the present invention and mixing them by a conventional method to form ointments. Examples of useful bases are liquid paraffin, white vaseline, bleached bee wax, octyldodecyl alcohol, paraffin, etc. Examples of useful preservatives are methyl para-hydroxybenzoate, ethyl para-hydroxybenzoate, propyl para-hydroxybenzoate, etc.

Attaching agents can be manufactured by applying the above-mentioned ointment, cream, gel, paste, or the like to conventional substrates by conventional methods. Examples of suitable substrates are woven fabric of cotton, staple fiber or artificial fiber, unwoven fabrics, film of soft vinyl chloride, polyethylene or polyurethane, and expanded sheet.

Examples of the "pharmaceutically acceptable carrier" added to the compound of formula (I) are various additives mentioned above in the pharmaceutical preparations.

The amount of the compound of the invention to be incorporated in the above-mentioned dosage unit form may vary depending on the patient's condition, dosage form, etc. In the case of compositions for oral administration or injections, about 0.1-200 mg of the compound of the invention is preferably incorporated into a dosage unit form. The daily dosage of the medicament in the above-mentioned forms varies depending on patient's condition, weight, age, sex, etc. but generally, it is preferably about 0.1-200 mg per adult. This amount is preferably administered once or in 2-4 divided doses.

EXAMPLES

The following experimental examples and examples are intended to illustrate the invention in further detail and should by no means be construed as limiting the scope of the invention.

Examples illustrate the synthesis of compounds according to the invention. Synthesis Examples illustrate the synthesis of the starting compound and intermediate for the production of the compound of the invention. ^{1}H-NMR means

hydrogen nuclear magnetic resonance spectrum, mp melting point, MS mass spectrometry, and IR infrared absorption spectrum.

A. Synthesis of diamide

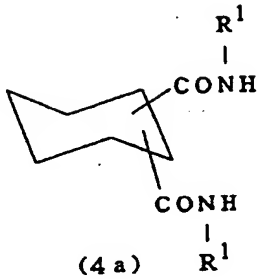
Synthesis Example 1

A 4.30 g quantity of trans-1,4-cyclohexanedicarbonic acid, 11.5 g of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride, 7.75 g of n-octylamine and 8.10 g of 1-hydroxybenzotriazole were dissolved in 200 ml of DMF and reacted at room temperature for 12 hours. The solvent was distilled off. The residue was extracted with ethyl acetate, washed with diluted hydrochloric acid, sodium carbonate and water in this order and dried over magnesium sulfate and the solvent was distilled off, thus giving 9.55 g (yield: 96.8%) of trans-1,4-cyclohexanedioctylamide.

Synthesis Examples 2-83

Diamide derivatives were prepared in the same manner as in Synthesis Example 1. Table 1 shows positions of the substituents of the diamide derivatives obtained in Synthesis Examples 1-83 and data on the results of measurement.

Table 1



(4a)

Synthesis Examples (Corresponding Example No.)	Position	R'	mp (℃)	IR(νNH, νC=O)
1(1)	trans-1,4	-n$(CH_2)_7CH_3$	230-238	3320, 1637
2(2)	trans-1,4	-n$(CH_2)_4CH_3$	271-278	3298, 1635
3(3)	trans-1,4	-n$(CH_2)_5CH_3$	185(dec)	3399, 1637
4(4)	trans-1,4	-n$(CH_2)_6CH_3$	232-239	3302, 1637
5(5)	trans-1,4	-n$(CH_2)_8CH_3$	226-234	3319, 1633
6(6)	trans-1,4	-n$(CH_2)_9CH_3$	225-230	3324, 1637
7(7)	trans-1,4	-$CH_2CCH_3)_3$	279-285	3290, 1647
8(8)	trans-1,4	-CH_2-cC_6H_{11}	285-295	3292, 1637
9(9)	trans-1,4	-$CH(CH_3)_2$	>300	3290, 1637
10(10)	trans-1,4	-$CH(CH_2CH_2CH_3)_2$.	>300	3288, 1637
11(11)	trans-1,4	-cC_5H_9	>300	3293, 1633
12(12~14-12)	trans-1,4	-cC_6H_{11}	>300	3294, 1637
13(15-25)	trans-1,4	-cC_7H_{13}	>300	3299, 1631
14(26)	trans-1,4	-cC_8H_{15}	>300	3267, 1633
15(27)	trans-1,4	-2-Norbornyl	>300	3284, 1635
16(28~28-3)	trans-1,4	-cC_6H_{10}-4-CH_3	>300	3298, 1635
17(29)	trans-1,4	-2-Adamantyl	268-272	3320, 1637

Table 1 (continued)

Synthesis Examples (Corresponding Example No.)	Position	R¹	mp (℃)	IR(ν NH, ν C=O)
18(30)	trans-1,4	-CH_2Ph	>300	3284,1637
19(31)	trans-1,4	-CH_2CH_2Ph	281-290	3299,1637
20(32)	trans-1,4	-CH_2CH_2-1-cHexenyl	275-278	3290,1635
21(33)	trans-1,4	-Furfuryl	>300	3320,1631
22(34)	cis-1,4	-n$(CH_2)_6CH_3$	52-56	3334,1643
23(35)	cis-1,4	-n$(CH_2)_7CH_3$	56-60	3334,1637
24(36)	cis-1,4	-n$(CH_2)_8CH_3$	52-57	3313,1635
25(37)	cis-1,4	-n$(CH_2)_9CH_3$	54-56	3311,1633
26(38)	cis-1,4	-$CH_2C(CH_3)_3$	201-207	2964,1647
27(39)	cis-1,4	-CH_2-cC_6H_{11}	147-150	3305,1645
28(40)	cis-1,4	-$CH(CH_2CH_2CH_3)_2$	151-155	3328,1639
29(41)	cis-1,4	-cC_5H_9	215-222	3284,1631
30(42)	cis-1,4	-cC_6H_{11}	154-158	2947,1635
31(43)	cis-1,4	-cC_7H_{13}	210-216	3298,1641
32(44)	cis-1,4	-cC_8H_{15}	160-182	2929,1639
33(45)	cis-1,4	-2-Norbornyl	244-245	3336,1641
34(46)	cis-1,4	-2-Adamantyl	294-300	3303,1641
35(47)	cis-1,4	-CH_2Ph	130-132	3326,1647
36(48)	cis-1,4	-CH_2CH_2Ph	105-106	3292,1635
37(49)	cis-1,4	-CH_2CH_2-1-cHexenyl	100-103	3319,1637
38(50)	cis-1,4	-Furfuryl	130-145	3305,1647
39(51)	trans-1,3	-n$(CH_2)_4CH_3$	94-96	3291,1637

Table 1 (continued)

Synthesis Examples (Corresponding Example No.)	Position	R'	mp (℃)	IR(νNH, νC=O)
40(52)	trans-1,3	-n$(CH_2)_5CH_3$	71-74	3296,1639
41(53)	trans-1,3	-n$(CH_2)_6CH_3$	75-79	3290,1637
42(54)	trans-1,3	-n$(CH_2)_7CH_3$	75-80	3313,1639
43(55)	trans-1,3	-n$(CH_2)_8CH_3$	80-82	3315,1639
44(56)	trans-1,3	-n$(CH_2)_9CH_3$	86-91	3307,1637
45(57)	trans-1,3	-CH_2-cC_6H_{11}	190-192	3291,1637
46(58)	trans-1,3	-$CH(CH_2CH_2CH_3)_2$	210-218	3292,1641
47(59)	trans-1,3	-cC_5H_9	230-239	3291,1635
48(60)	trans-1,3	-cC_6H_{11}	230-235	3296,1637
49(61)	trans-1,3	-cC_7H_{13}	236-239	3298,1637
50(62)	trans-1,3	-2-Norbornyl	252-258	3322,1639
51(63)	trans-1,3	-cC_6H_{10}-4-CH_3	206-212	3284,1639
52(64)	trans-1,3	-CH_2Ph	105-109	3286,1643
53(65)	trans-1,3	-CH_2CH_2Ph	106-109	3320,1643
54(66)	trans-1,3	-CH_2CH_2-cHexenyl	125-130	3280,1637
55(67)	cis-1,3	-n$(CH_2)_4CH_3$	225-227	3291,1639
56(68)	cis-1,3	-n$(CH_2)_5CH_3$	209-214	3286,1639
57(69)	cis-1,3	-n$(CH_2)_6CH_3$	208-211	3292,1639
58(70)	cis-1,3	-n$(CH_2)_7CH_3$	175-181	3292,1639
59(71)	cis-1,3	-n$(CH_2)_8CH_3$	198-201	3298,1639
60(72)	cis-1,3	-n$(CH_2)_9CH_3$	194-197	3301,1639
61(73)	cis-1,3	-$CH_2C(CH_3)_3$	252-261	3292,1644

Table 1 (continued)

Synthesis Examples (Corresponding Example No.)	Position	R'	mp (℃)	IR(ν NH, ν C=O)
62(74)	cis-1,3	$-CH_2-cC_6H_{11}$	245-249	3295,1639
63(75)	cis-1,3	$-CH(CH_3)_2$	279-290	3292,1639
64(76)	cis-1,3	$-CH(CH_2CH_3)_2$	272-281	3282,1642
65(77)	cis-1,3	$-CH(CH_2CH_2CH_3)_2$	258-266	3322,1637
66(78)	cis-1,3	$-cC_5H_9$	>300	3272,1631
67(79-82)	cis-1,3	$-cC_6H_{11}$	299-306	3299,1639
68(83)	cis-1,3	$-cC_7H_{13}$	>300	3298,1637
69(84)	cis-1,3	$-cC_8H_{15}$	291-295	3245,1633
70(85)	cis-1,3	-2-Norbornyl	>300	3282,1637
71(86)	cis-1,3	$-CH_2Ph$	195(dec)	3294,1637
72(87)	cis-1,3	$-CH_2CH_2Ph$	251-253	3292,1639
73(88)	cis-1,3	$-CH_2CH_2$-1-cHexenyl	221-228	3288,1641
74(89)	cis-1,3	-Furfuryl	230-237	3293,1641
75(90)	cis-1,2	$-n(CH_2)_6CH_3$	112-115	3299,1643
76(91)	trans-1,2	$-cC_6H_{11}$	284-286	3309,1641
77(92)	trans-1,2	$-cC_7H_{13}$	277-281	3294,1639
78(93)	trans-1,2	$-CH_2Ph$	219-225	3268,1645
79(94)	trans-1,2	$-n(CH_2)_6CH_3$	173-185	3299,1644
80(95)	cis-1,2	$-CH_2-cC_6H_{11}$	178-181	3276,1641
81(96)	cis-1,2	$-cC_6H_{11}$	266-268	2929,1639
82(97)	cis-1,2	$-cC_7H_{13}$	253-257	3251,1639
83(98)	cis-1,2	-Furfuryl	132-136	3282,1644

B. Synthesis of diamine

Preparation Example 1

Lithiumaluminum hydride, 2.17 g, was added little by little under ice-cooling to 150 ml of a THF suspension containing 8.70 g of the diamide derivative prepared in Synthesis Example 1. Stirring was continued for 1 hour and the reaction mixture was refluxed with heating for 65 hours. After adding 4.3 ml of water and 4.3 ml of a 2N aqueous sodium hydroxide solution under ice-cooling, the reaction mixture was allowed to stand at room temperature for 15 hours. The reaction

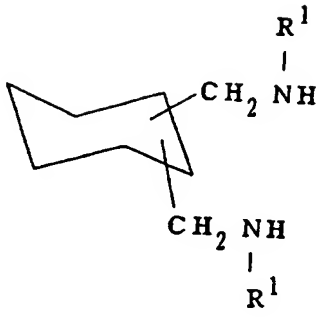
mixture was filtered with suction and the filtrate was concentrated under reduced pressure. The residue was dissolved in hexane and washed with a saturated aqueous sodium bicarbonate solution and saturated brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide 5.03 g (yield: 76.2%) of a diamine derivative as a viscous oil compound.

Preparation Examples 2-83

Diamine derivatives were prepared in the same manner as in Preparation Example 1.

Table 2 shows positions of the substituents of the diamine derivatives obtained in Preparation Examples 1-83 and data on the results of measurement.

Table 2



Synthesis Examples (Corresponding Example No.)	Position	R'	IR(ν)	NMR(DMSO-d6) δ : (CH_2NHR')
1(1)	trans-1,4	-n$(CH_2)_7CH_3$	1452, 2924	2.31
2(2)	trans-1,4	-n$(CH_2)_4CH_3$	1450, 2924	2.31
3(3)	trans-1,4	-n$(CH_2)_5CH_3$	1450, 2929	2.36
4(4)	trans-1,4	-n$(CH_2)_6CH_3$	1454, 2927	2.31
5(5)	trans-1,4	-n$(CH_2)_8CH_3$	1448, 2922	2.31
6(6)	trans-1,4	-n$(CH_2)_9CH_3$	1448, 2922	2.31
7(7)	trans-1,4	-$CH_2C(CH_3)_3$	1462, 2912	2.36
8(8)	trans-1,4	-CH_2-cC_6H_{11}	1446, 2915	2.30
9(9)	trans-1,4	-$CH(CH_3)_2$	1448, 2920	2.32
10(10)	trans-1,4	-$CH(CH_2CH_2CH_3)_2$	1466, 2924	2.31
11(11)	trans-1,4	-cC_5H_9	1444, 2914	2.31
12(12~14-12)	trans-1,4	-cC_6H_{11}	1454, 2913	2.34
13(15-25)	trans-1,4	-cC_7H_{13}	1460, 2925	2.32
14(26)	trans-1,4	-cC_8H_{15}	1448, 2924	2.31
15(27)	trans-1,4	-2-Norbornyl	1448, 2949	2.32
16(28~28-3)	trans-1,4	-cC_6H_{10}-4-CH_3	1441, 2918	2.31
17(29)	trans-1,4	-2-Adamantyl	1446, 2906	2.35

Table 2 (continued)

Synthesis Examples (Corresponding Example No.)	Position	R'	IR(ν)	NMR(DMSO-d6) δ:(CH_2NHR')
18(30)	trans-1,4	-CH_2Ph	1450, 2929	2.33
19(31)	trans-1,4	-CH_2CH_2Ph	1452, 2916	2.36
20(32)	trans-1,4	-CH_2CH_2-1-cHexenyl	1466, 2922	2.33
21(33)	trans-1,4	-Furfuryl	1448, 2916	2.33
22(34)	cis-1,4	-n$(CH_2)_6CH_3$	1456, 2925	2.38
23(35)	cis-1,4	-n$(CH_2)_7CH_3$	1463, 2923	2.39
24(36)	cis-1,4	-n$(CH_2)_8CH_3$	1464, 2924	2.39
25(37)	cis-1,4	-n$(CH_2)_9CH_3$	1466, 2924	2.38
26(38)	cis-1,4	-$CH_2C(CH_3)_3$	1463, 2950	2.43
27(39)	cis-1,4	-CH_2-cC_6H_{11}	1448, 2922	2.31
28(40)	cis-1,4	-$CH(CH_2CH_2CH_3)_2$	1466, 2929	2.39
29(41)	cis-1,4	-cC_5H_9	1450, 2922	2.38
30(42)	cis-1,4	-cC_6H_{11}	1450, 2927	2.45
31(43)	cis-1,4	-cC_7H_{13}	1448, 2924	2.43
32(44)	cis-1,4	-cC_8H_{15}	1448, 2924	2.40
33(45)	cis-1,4	-2-Norbornyl	1448, 2952	2.37
34(46)	cis-1,4	-2-Adamantyl	1444, 2906	2.42
35(47)	cis-1,4	-CH_2Ph	1452, 2922	2.38
36(48)	cis-1,4	-CH_2CH_2Ph	1454, 2922	2.44
37(49)	cis-1,4	-CH_2CH_2-1-cHexenyl	1448, 2924	2.40
38(50)	cis-1,4	-Furfuryl	1450, 2924	2.40
39(51)	trans-1,3	-n$(CH_2)_4CH_3$	1460, 2929	2.39

Table 2 (continued)

Synthesis Examples (Corresponding Example No.)	Position	R'	IR(ν)	NMR(DMSO-d6) δ : (CH_2NHR')
40(52)	trans-1,3	-n$(CH_2)_5CH_3$	1461, 2927	2.38
41(53)	trans-1,3	-n$(CH_2)_6CH_3$	1459, 2927	2.38
42(54)	trans-1,3	-n$(CH_2)_7CH_3$	1464, 2925	2.40
43(55)	trans-1,3	-n$(CH_2)_8CH_3$	1463, 2924	2.38
44(56)	trans-1,3	-n$(CH_2)_9CH_3$	1464, 2925	2.38
45(57)	trans-1,3	-CH_2-cC_6H_{11}	1448, 2921	2.31
46(58)	trans-1,3	-$CH(CH_2CH_2CH_3)_2$	1460, 2952	2.38
47(59)	trans-1,3	-cC_5H_9	1450, 2929	2.39
48(60)	trans-1,3	-cC_6H_{11}	1450, 2929	2.41
49(61)	trans-1,3	-cC_7H_{13}	1460, 2925	2.38
50(62)	trans-1,3	-2-Norbornyl	1462, 2952	2.36
51(63)	trans-1,3	-cC_6H_{10}-4-CH_3	1450, 2924	2.38
52(64)	trans-1,3	-CH_2Ph	1454, 2923	2.38
53(65)	trans-1,3	-CH_2CH_2Ph	1454, 2925	2.42
54(66)	trans-1,3	-CH_2CH_2-cHexenyl	1448, 2925	2.38
55(67)	cis-1,3	-n$(CH_2)_4CH_3$	1458, 2927	2.31
56(68)	cis-1,3	-n$(CH_2)_5CH_3$	1458, 2925	2.31
57(69)	cis-1,3	-n$(CH_2)_6CH_3$	1458, 2927	2.32
58(70)	cis-1,3	-n$(CH_2)_7CH_3$	1448, 2927	2.32
59(71)	cis-1,3	-n$(CH_2)_8CH_3$	1458, 2927	2.31
60(72)	cis-1,3	-n$(CH_2)_9CH_3$	1458, 2923	2.32
61(73)	cis-1,3	-$CH_2C(CH_3)_3$	1462, 2920	2.35

Table 2 (continued)

Synthesis Examples (Corresponding Example No.)	Position	R'	IR(ν)	NMR(DMSO-d6) δ : (CH_2NHR')
62(74)	cis-1,3	$-CH_2-cC_6H_{11}$	1460, 2916	2.30
63(75)	cis-1,3	$-CH(CH_3)_2$	1471, 2922	2.32
64(76)	cis-1,3	$-CH(CH_2CH_3)_2$	1459, 2924	2.32
65(77)	cis-1,3	$-CH(CH_2CH_2CH_3)_2$	1459, 2924	2.34
66(78)	cis-1,3	$-cC_5H_9$	1448, 2922	2.31
67(79-82)	cis-1,3	$-cC_6H_{11}$	1450, 2925	2.35
68(83)	cis-1,3	$-cC_7H_{13}$	1448, 2925	2.31
69(84)	cis-1,3	$-cC_8H_{15}$	1446, 2922	2.31
70(85)	cis-1,3	-2-Norbornyl	1450, 2943	2.31
71(86)	cis-1,3	$-CH_2Ph$	1454, 2920	2.32
72(87)	cis-1,3	$-CH_2CH_2Ph$	1454, 2922	2.35
73(88)	cis-1,3	$-CH_2CH_2$-1-cHexenyl	1446, 2922	2.32
74(89)	cis-1,3	-Furfuryl	1448, 2924	2.33
75(90)	cis-1,2	$-n(CH_2)_6CH_3$	1448, 2929	2.42
76(91)	trans-1,2	$-cC_6H_{11}$	1448, 2925	2.36
77(92)	trans-1,2	$-cC_7H_{13}$	1448, 2929	2.35
78(93)	trans-1,2	$-CH_2Ph$	1452, 2922	2.36
79(94)	trans-1,2	$-n(CH_2)_6CH_3$	1448, 2927	2.37
80(95)	cis-1,2	$-CH_2-cC_6H_{11}$	1448, 2924	2.44
81(96)	cis-1,2	$-cC_6H_{11}$	1450, 2929	2.33
82(97)	cis-1,2	$-cC_7H_{13}$	1448, 2925	2.32
83(98)	cis-1,2	-Furfuryl	1448, 2925	2.40

Example 1

Trans-1,4-bis[3-(4-dimethylaminophenyl)-1-normaloctylureido]methyl]cyclohexane

A 1.28 g quantity of phenyl 4-dimethylaminophenylcarbamate, 0.28 g of tetrabutylammonium bromide (TBAB) and 0.33 g of potassium hydroxide were added to a solution of 0.73 g of trans-1,4-bis[(normaloctylamino)methyl]cyclohexane in 30 ml of acetonitrile and stirred at room temperature for 15 hours. After completion of the reaction, the crystals precipitated were separated by filtration and washed with ether, water and hexane. After purifying the crystals by silica gel column chromatography, the crystals were dissolved in chloroform and a 4N hydrochloric acid-dioxane solution was added to provide 1.21 g (yield: 79%) of white crystals precipitated.
mp: 185-189°C (dihydrochloric acid salt)
MS(FAB): m/e = 647 (M^++1)
IR(KBr) ν MAX: 2923, 2366(brs), 1644(s), 1521(s)
NMR(DMSO-d_6) δ: 8.27 (2H, brs, NH x 2), 7.4-7.6 (8H, br, Ar-H), 3.28 (4H, brs, NCH_2 x 2), 3.16 (4H, br, NCH_2 x 2), 3.05 (4H, br, $N(CH_3)_2$ x 2), 1.2-1.8 (32H, m), 0.8-1.0 (8H, m)

Elemental analysis (for $C_{42}H_{70}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 64.51;	H, 9.54;	N, 10.75.
Found (%):	C, 64.72;	H, 9.33;	N, 10.68.

Example 2

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-normalpentylureido]methyl]cyclohexane

Trans-1,4-bis[(normalpentylamino)methyl]cyclohexane, 0.56 g, was dissolved in 10 ml of ether. A solution of 0.81 g of 4-dimethylaminophenyl isocyanate in 20 ml of acetonitrile was added. The reaction mixture was stirred at room temperature for 10 hours. The solvent of the reaction mixture was distilled off under reduced pressure and the residue was purified by silica gel column chromatography to provide 1.10 g (yield: 89%) of white crystals.
mp: 205-208°C (free form)
MS(FAB): m/e = 607 (M^++1)
IR(KBr) ν MAX: 2912, 1633(s), 1519(s)
NMR(DMSO-d_6) δ: 7.66 (2H, s, NH x 2), 7.20 (4H, d, J=9.2Hz, Ar-H), 6.63 (4H, d, J=9.2Hz, Ar-H), 3.1-3.3 (8H, m, NCH_2 x 2, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.2-1.8 (18H, m), 0.8-1.0 (10H, m)

Elemental analysis (for $C_{36}H_{58}N_6O_2 \cdot 2H_2O$)			
Calculated (%):	C, 67.25;	H, 9.72;	N, 13.07.
Found (%):	C, 66.77;	H, 9.94;	N, 12.83.

Example 3

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-normalhexylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 160-163°C (dihydrochloric acid salt)
MS(FAB): m/e = 635 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1646(s), 1521(s)
NMR(DMSO-d_6) δ: 8.27 (2H, brs, NH x 2), 7.50-7.70 (8H, brs,

Ar-H), 3.0-3.4 (20H, br, NCH_2 x 2, NCH_2 x 2, $N(CH_3)_2$ x 2), 1.2-1.8 (24H, m), 0.8-1.0 (8H, m)

Elemental analysis (for $C_{38}H_{62}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 62.88;	H, 9.16;	N, 11.58.
Found (%):	C, 62.60;	H, 9.40;	N, 11.86.

Example 4

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-normalheptylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 189-191°C (dihydrochloric acid salt)
MS(FAB): m/e = 662 (M^+)
IR(KBr) ν MAX: 2925(brs), 1648(s), 1521(s)
NMR(DMSO-d_6) δ: 8.32 (2H, s, NH x 2), 7.4-7.7 (8H, m, Ar-H), 3.33 (4H, m, NCH_2 x 2), 3.22 (4H, m, NCH_2 x 2), 3.10 (12H, s, $N(CH_3)_2$ x 2), 1.5-1.8 (10H, m), 1.2-1.4 (16H, m), 0.8-1.0 (10H, m)

Elemental analysis (for $C_{40}H_{66}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 63.72;	H, 9.35;	N, 11.15.
Found (%):	C, 63.91;	H, 9.69;	N, 11.10.

Example 5

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-normalnonyl ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 220-223°C (dihydrochloric acid salt)
MS(FAB): m/e = 719 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1643(s), 1521(s)
NMR(DMSO-d_6) δ: 8.23 (2H, brs, NH x 2), 7.4-7.6 (8H, br, Ar-H), 3.28 (4H, t, J = 7.0 Hz, NCH_2 x 2), 3.16 (4H, d, J = 7.3 Hz, NCH_2 x 2), 3.04 (12H, s, $N(CH_3)_2$ x 2), 1.2-1.8 (36H, m), 0.8-1.0 (8H, m)

Elemental analysis (for $C_{44}H_{74}N_6O_2 \cdot 2HCl \cdot 1/2H_2O$)			
Calculated (%):	C, 65.98;	H, 9.69;	N, 10.49.
Found (%):	C, 66.05;	H, 9.43;	N, 10.42.

Example 6

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-normaldecylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 155-160°C (dihydrochloric acid salt)
MS(FAB): m/e = 746 (M^+)
IR(KBr) ν MAX: 2921, 2979(brs), 1671(s), 1643(s)
NMR(DMSO-d_6) δ: 8.28 (2H, brs, NH x 2), 7.4-7.7 (8H, br, Ar-H), 3.28 (4H, br, NCH_2 x 2), 3.16 (4H, br, NCH_2 x 2), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.4-1.8 (8H, m), 1.2-1.3 (32H, m), 0.92 (2H, m), 0.85 (6H, t, J = 7.0 Hz, CH_3 x 2)

Elemental analysis (for $C_{46}H_{78}N_6O_2 \cdot 2HCl \cdot 1/2H_2O$)			
Calculated (%):	C, 66.64;	H, 9.85;	N, 10.14.
Found (%):	C, 66.48;	H, 10.02;	N, 10.39.

Example 7

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-neopentylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 196-198°C (dihydrochloric acid salt)
MS(FAB): m/e = 607 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1652(s), 1519(s)
NMR(DMSO-d_6) δ: 8.44 (2H, s, NH x 2), 7.55 (8H, br, Ar-H), 3.0-3.3 (20H, m, NCH_2 x 4, $N(CH_3)_2$ x 2), 1.5-1.7 (6H, m), 0.8-1.0 (22H, m)

Elemental analysis (for $C_{36}H_{58}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 61.96;	H, 8.96;	N, 12.04.
Found (%):	C, 61.90;	H, 8.77;	N, 12.20.

Example 8

Trans-1,4-bis[[1-cyclohexylmethyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 210-212°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2919(brs), 1656(s), 1513(s)
NMR(DMSO-d_6) δ: 8.25 (2H, s, NH x 2), 7.4-7.7 (8H, s, Ar-H), 3.1-3.3 (20H, m, NCH_2 x 4, $N(CH_3)_2$ x 2), 1.5-1.7 (24H, m), 1.0-1.3 (4H, m), 0.8-1.0 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 63.31;	H, 8.90;	N, 11.07.
Found (%):	C, 63.38;	H, 8.84;	N, 11.23.

Example 9

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-isopropylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 204-207°C (dihydrochloric acid salt)
MS(FAB): m/e = 551 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1635(s), 1448(s)
NMR(DMSO-d_6) δ: 8.33 (2H, s, NH x 2), 7.56 (8H, br, Ar-H), 4.20 (2H, m, NCH x 2), 3.0-3.2 (16H, NCH_2 x 2, $N(CH_3)_2$ x 2), 1.5-1.7 (6H, m), 1.14 (12H, d, J = 6.6Hz, $CH(CH_3)_2$ x 2), 0.8-1.0 (4H, m)

Elemental analysis (for $C_{32}H_{54}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 59.89;	H, 8.48;	N, 13.10.
Found (%):	C, 59.60;	H, 8.48;	N, 13.38.

Example 10

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-(4-heptyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 173-176°C (free form)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2964(s), 1623(s), 1592(s), 1521(s)
NMR(DMSO-d_6) δ: 7.57 (2H, s, NH x 2), 7.18 (4H, d, J = 9.0Hz Ar-H), 6.62 (4H, d, J = 9.0Hz, Ar-H), 3.92 (2H, s, NCH x 2), 2.97 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.2-1.8 (24H, m), 0.8-1.0 (16H, m)

Elemental analysis (for $C_{40}H_{66}N_6O_2$)			
Calculated (%):	C, 72.46;	H, 10.03;	N, 12.68.
Found (%):	C, 72.12;	H, 10.22;	N, 12.49.

Example 11

Trans-1,4-bis[[1-cyclopentyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 202-204°C (dihydrochloric acid salt)

MS(FAB): m/e = 602 (M^+)
IR(KBr) ν MAX: 2915(brs), 1631(s), 1519(s)
NMR(DMSO-d_6) δ: 8.34 (2H, s, NH x 2), 7.56 (8H, s, Ar-H), 4.17 (2H, m, NCH x 2), 3.10 (4H, d, J = 7.0Hz, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.5-1.8 (22H, m), 0.8-1.0 (4H, m)

Elemental analysis (for $C_{38}H_{54}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 62.32;	H, 8.43;	N, 12.11.
Found (%):	C, 61.80;	H, 8.96;	N, 12.00.

Example 12

Trans-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 200-202°C (dihydrochloric acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1652(s), 1519(s)
NMR(DMSO-d_6) δ: 8.34 (2H, s, NH x 2), 7.56 (8H, brs, Ar-H), 3.82 (2H, m, NCH x 2), 3.09 (4H, d, J = 7.0Hz, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 62.45;	H, 8.69;	N, 11.50.
Found (%):	C, 62.31;	H, 8.82;	N, 11.40.

Example 12-1

Trans-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 145-147°C (fumaric acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2922(brs), 1626(s), 1518(s)
NMR(DMSO-d_6) δ: 7.66 (2H, s, NH x 2), 7.18 (4H, d, J = 9.2Hz, Ar-H), 6.63 (4H, d, J = 9.2Hz, Ar-H), 6.62 (2H, s, = CH x 2), 3.78 (2H, br, NCH x 2), 3.03 (4H, d, J = 6.9Hz, NCH_2 x 2),
2.81 (12H, s, $N(CH_3)_2$ x 2), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot C_4H_4O_4 \cdot H_2O$)			
Calculated (%):	C, 65.94;	H, 8.43;	N, 10.99.
Found (%):	C, 65.81;	H, 8.62;	N, 10.76.

Example 12-2

Trans-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 128-131°C (maleic acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1633(s), 1518(s)
NMR(DMSO-d_6) δ: 7.66 (2H, s, NH x 2), 7.19 (4H, d, J = 9.2Hz, Ar-H), 6.63 (4H, d, J = 9.2Hz, Ar-H), 6.19 (2H, s, = CH x 2), 3.79 (2H, br, NCH x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 2.83 (12H, s, $N(CH_3)_2$ x 0.8-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot C_4H_4O_4 \cdot 1/2H_2O$)			
Calculated (%):	C, 66.73;	H, 8.46;	N, 11.12.
Found (%):	C, 66.75;	H, 8.04;	N, 10.90.

Example 12-3

Trans-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 110-115°C (dimethanesulfonic acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2922(brs), 1637(s), 1517(s)
NMR(DMSO-d_6) δ: 8.20 (2H, br, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.80 (2H, br, NCH x 2), 3.0-3.2 (16H, br), 2.38 (6H, s, SCH_3 x 2), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot 2CH_4O_3S \cdot 3H_2O$)			
Calculated (%):	C, 54.78;	H, 8.27;	N, 9.58.
Found (%):	C, 54.49;	H, 8.43;	N, 9.76.

Example 13

Trans-1,4-bis[[1-cyclohexyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 174-178°C (dihydrochloric acid salt)
MS(FAB): m/e = 711 (M^++1)
IR(KBr) ν MAX: 2938(brs), 1648(s), 1515(s)
NMR(DMSO-d_6) δ: 8.34 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.80 (2H, m, NCH x 2), 3.4-3.5 (8H, $N(CH_3)_2$ x 2), 3.09 (4H, d, J = 7.3Hz, NCH_2 x 2), 0.8-1.8 (42H, m)

Elemental analysis (for $C_{44}H_{66}N_6O_2 \cdot 2HCl \cdot 5/2H_2O$)			
Calculated (%):	C, 63.75;	H, 8.88;	N, 10.14.
Found (%):	C, 63.83;	H, 8.85;	N, 9.79.

Example 14

Trans-1,4-bis[[1-cyclohexyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 212-217°C (dihydrochloric acid salt)
MS(FAB): m/e = 686 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1629(s), 1521(s)
NMR(DMSO-d_6) δ: 8.39 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.81 (2H, m, NCH x 2), 3.4-3.6 (8H, $N(CH_2)_2$ x 2), 3.09 (4H, d, J = 7.0Hz, NCH_2 x 2), 0.8-1.8 (42H, m)

Elemental analysis (for $C_{46}H_{66}N_6O_2 \cdot 2HCl \cdot 9/2H_2O$)			
Calculated (%):	C, 59.98;	H, 9.22;	N, 9.99.
Found (%):	C, 59.79;	H, 8.80;	N, 9.87.

Example 14-1

Trans-1,4-bis[[1-cyclohexyl-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 149-152°C (dihydrochloric acid salt)
MS(FAB): m/e = 683 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1645(s), 1518(s)
NMR(DMSO-d_6) δ: 8.18 (2H, br, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.80 (2H, br, NCH x 2), 3.59 (8H, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-2.2 (38H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 63.70;	H, 8.65;	N, 10.61.
Found (%):	C, 63.70;	H, 8.34;	N, 10.63.

Example 14-2

Trans-1,4-bis[[1-cyclohexyl-3-(4-homopiperidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 132-135°C (dihydrochloric acid salt)

MS(FAB): m/e = 739 (M^++1)
IR(KBr) ν MAX: 2918(brs), 1655(s), 1518(s)
NMR(DMSO-d_6) δ: 7.87 (2H, br, NH x 2), 6.8-7.4 (8H, br, Ar-H), 3.80 (2H, br, NCH x 2), 3.4-3.7 (8H, m, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-1.8 (46H, m)

Elemental analysis (for $C_{42}H_{70}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 65.15;	H, 9.03;	N, 9.91.
Found (%):	C, 65.43;	H, 9.02;	N, 9.95.

Example 14-3

Trans-1,4-bis[[1-cyclohexyl-3-(4-heptamethyleneiminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 126-130°C (dihydrochloric acid salt)
MS(FAB): m/e = 767 ($M+_{+1}$)
IR(KBr) ν MAX: 2922(brs), 1635(s), 1522(s)
NMR(DMSO-d_6) δ: 7.95 (2H, br, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.78 (2H, br, NCH x 2), 3.49 (8H, m, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-2.0 (50H, m)

Elemental analysis (for $C_{48}H_{74}N_6O_2 \cdot 2HCl \cdot 5/2H_2O$)			
Calculated (%):	C, 64.47;	H, 9.06;	N, 9.81.
Found (%):	C, 64.28;	H, 8.79;	N, 9.79.

Example 14-4

Trans-1,4-bis[[1-cyclohexyl-3-(4-morpholinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 156-158°C (dihydrochloric acid salt)
MS(FAB): m/e = 715 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1641(s), 1518(s)
NMR(DMSO-d_6) δ: 8.18 (2H, br, NH x 2), 7.3-7.6 (8H, br, Ar-H), 3.97 (8H, brs, $O(CH_2)_2$ x 2), 3.80 (2H, m, NCH x 2), 3.35 (8H, brs, $N(CH_2)_2$ x 2), 3.08 (4H, d, J = 6.9Hz, NCH_2 x 2), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_4 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 59.92;	H, 8.38;	N, 9.98.
Found (%):	C, 59.80;	H, 8.09;	N, 9.96.

Example 14-5

Trans-1,4-bis[[1-cyclohexyl-3-(4-methylpiperadinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 205-212°C (tetrahydrochloric acid salt)
MS(FAB): m/e = 741 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1630(s), 1520(s)
NMR(DMSO-d_6) δ: 7.86 (2H, br, NH x 2), 7.30 (4H, d, J = 8.8Hz, Ar-H), 6.87 (4H, d, J = 8.8Hz, Ar-H), 3.0-3.8 (22H, m), 2.79 (6H, s, NCH_3 x 3), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{44}H_{68}N_8O_2 \cdot 4HCl \cdot 2H_2O$)			
Calculated (%):	C, 57.26;	H, 8.08;	N, 12.14.
Found (%):	C, 57.26;	H, 8.00;	N, 11.94.

Example 14-6

Trans-1,4-bis[[1-cyclohexyl-3-(4-diisobutylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 140-142°C (dihydrochloric acid salt)
MS(FAB): m/e = 799 (M^++1)
IR(KBr) ν MAX: 2931(brs), 1627(s), 1520(s)
NMR(DMSO-d_6) δ: 8.20 (2H, br, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.80 (2H, br, NCH x 2), 3.4-3.7 (8H, m, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-2.2 (58H, m)

Elemental analysis (for $C_{50}H_{82}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 66.13;	H, 9.77;	N, 9.25.
Found (%):	C, 66.37;	H, 10.01;	N, 9.20.

Example 14-7

Trans-1,4-bis[[1-cyclohexyl-3-(4-dinormalpropylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 147-150°C (dihydrochloric acid salt)
MS(FAB): m/e = 743 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1637(s), 1518(s)
NMR(DMSO-d_6) δ: 8.18 (2H, br, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.78 (2H, br, NCH x 2), 3.4-3.7 (8H, m, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-1.8 (50H, m)

Elemental analysis (for $C_{46}H_{74}N_6O_2 \cdot 2HCl \cdot 4H_2O$)			
Calculated (%):	C, 62.21;	H, 9.53;	N, 9.46.
Found (%):	C, 62.10;	H, 9.70;	N, 9.46.

Example 14-8

Trans-1,4-bis[[1-cyclohexyl-3-(4-aminophenyl)ureido]methyl]cyclohexane

A 0.6 g quantity of 10% palladium carbon was added to 100 ml of a DMF solution containing 5.7 g of trans-1,4-bis[[1-cyclohexyl-3-(4-nitrophenyl)ureido]-metyl]cyclohexane synthesized in accordance with Example 2. Hydrogen was added at ordinal pressure and normal temperature for 15 hours. After completion of the reaction, palladium was separated by filtration and the reaction mixture was concentrated under reduced pressure. The reaction mixture was dissolved in chloroform and a 4N hydrochloric acid-dioxyane solution was added to provide 5.5 g (95%) of white crystals precipitated.

mp: 185-188°C (dihydrochloric acid salt)

MS(FAB): m/e = 575 (M^++1)

IR(KBr) ν MAX: 2927(brs), 1520(s)

NMR(DMSO-d_6) δ: 9.92 (6H, br, N^+H_3 x 2), 8.22 (2H, brs, NH x 2), 7.50 (4H, d, J = 8.8Hz, Ar-H), 7.20 (4H, d, J = 8.8Hz, Ar-H), 3.79 (2H, m, NCH x 2), 3.08 (4H, d, J = 7.3Hz, NCH_2 x 2), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{34}H_{50}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 59.73;	H, 8.26;	N, 12.29.
Found (%):	C, 59.49;	H, 8.55;	N, 12.41.

Example 14-9

Trans-1,4-bis[[1-cyclohexyl-3-(4-acetaminophenyl)ureido]methyl]cyclohexane

A 0.25 g quantity of acetic anhydride and 0.25 g of triethylamine were added to 100 ml of a chloroform solution containing 0.58 g of trans-1,4-bis[[1-cyclohexyl-3-(4-aminophenyl)ureido]metyl]cyclohexane (free form) obtained in Example 14-8, and stirred at normal temperature for 3 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and distilled water was added to the residue. The crystals precipitated were washed with ether and dried under reduced pressure to provide 0.60 g (90%) of white crystals.

mp: 228-231°C

MS(FAB): m/e = 658 (M^+)

IR(KBr) ν MAX: 2927(brs), 1637(s), 1512(s)

NMR(DMSO-d_6) δ: 8.20 (2H, br, NH x 2), 7.2-7.5 (8H, br, Ar-H), 3.76 (2H, m, NCH x 2), 3.05 (4H, d, J = 6.9HZ, NCH_2 x 2), 1.99 (6H, s, NCH_3), 0.8-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{54}N_6O_4$)			
Calculated (%):	C, 69.27;	H, 8.26;	N, 12.76.
Found (%):	C, 69.43;	H, 8.41;	N, 12.59.

Example 14-10

Trans-1,4-bis[[1-cyclohexyl-3-(4-imidazolophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 253-260°C (dihydrochloric acid salt)
MS(FAB): m/e = 677 (M^++1)
IR(KBr) ν MAX: 2866(brs), 1635(s), 1525(s)
NMR(DMSO-d_6) δ: 8.1-8.5 (4H, m), 7.5-7.6 (10H, br), 6.47 (2H, s, Imidazolyl-H x 2), 3.80 (2H, m, NCH x 2), 3.09 (4H, d, J = 7.3HZ, NCH_2 x 2), 0.8-2.2 (30H, m)

Elemental analysis (for $C_{40}H_{52}N_8O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 61.85;	H, 7.14;	N, 14.43.
Found (%):	C, 62.03;	H, 7.01;	N, 14.52.

Example 14-11

Trans-1,4-bis[[1-cyclohexyl-3-(4-ethylmethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 151-153°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1635(s), 1515(s)
NMR(DMSO-d_6) δ: 8.26 (2H, br, NH x 2), 7.2-7.7 (8H, m, Ar-H), 3.79 (2H, m, NCH x 2), 3.48 (4H, m, NCH_2 x 2), 3.0-3.2 (10H, br), 0.8-1.8 (36H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 62.57;	H, 8.93;	N, 10.95.
Found (%):	C, 62.39;	H, 9.15;	N, 10.86.

Example 14-12

Trans-1,4-bis[[1-cyclohexyl-3-(4-methylpropylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 151-153°C (dihydrochloric acid salt)

MS(FAB): m/e = 687 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1631(s), 1522(s)
NMR(DMSO-d_6) δ: 8.30 (2H, br, NH x 2), 7.2-7.5 (8H, m, Ar-H), 3.80 (2H, br, NCH x 2), 3.3-3.5 (4H, m, NCH_2 x 2), 3.0-3.2 (10H, br, NCH_2 x 2), 0.8-1.8 (40H, m)

Elemental analysis (for $C_{42}H_{66}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 63.38;	H, 9.12;	N, 10.56.
Found (%):	C, 63.70;	H, 8.98;	N, 10.24.

Example 15

Trans-1,4-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 159-164°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2917(brs), 1643(s), 1631(s), 1513(s)
NMR(DMSO-d_6) δ: 8.26 (2H, s, NH x 2), 7.4-7.7 (8H, m, Ar-H), 3.78 (2H, m, NCH x 2), 3.0-3.2 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.3-1.8 (30H, m, CH_2 x 15), 0.8-1.0 (4H, m, CH_2 x 2)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 61.13;	H, 8.98;	N, 10.69.
Found (%):	C, 61.28;	H, 9.16;	N, 10.92.

Example 16

Trans-1,4-bis[[1-cycloheptyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 175-178°C (dihydrochloric acid salt)
MS(FAB): m/e = 738 ($M+_{+1}$)
IR(KBr) ν MAX: 2927(brs), 1646(s), 1637(s), 1515(s) NMR(DMSO-d_6) δ: 8.29 (2H, brs, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.78 (2H, m, NCH x 2), 3.2-3.6 (8H, br, NCH_2 x 2), 3.09 (4H, d, J = 7.0Hz, NCH_2 x 2), 1.4-2.4 (42H, m), 0.90 (4H, m)

Elemental analysis (for $C_{46}H_{70}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 66.56;	H, 8.99;	N, 10.13.
Found (%):	C, 66.48;	H, 9.23;	N, 10.08.

Example 17

Trans-1,4-bis[[1-cycloheptyl-3-(3-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 151-156°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2919(brs), 1641(s), 1604(s), 1506(s)
NMR(DMSO-d_6) δ: 8.32 (2H, brs, NH x 2), 7.74 (2H, brs, Ar-H), 7.1-7.4 (6H, m, Ar-H), 3.80 (2H, m, NCH x 2), 3.09 (4H, d, J = 7.3Hz, NCH_2 x 2), 3.04 (12H, s, $N(CH_3)_2$ x 2), 1.4-1.8 (30H, m), 0.91 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 64.07;	H, 8.87;	N, 11.21.
Found (%):	C, 64.32;	H, 9.10;	N, 10.98.

Example 18

Trans-1,4-bis[[1-cycloheptyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 170-175°C (dihydrochloric acid salt)
MS(FAB): m/e = 715 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1639(s), 1612(s), 1515(s)
NMR(DMSO-d_6) δ: 8.33 (2H, brs, NH x 2), 7.61 (8H, brs, Ar-H), 3.78 (2H, m, NCH x 2), 3.3-3.6 (8H, br, NCH_2 x 4), 3.09 (4H, d, J = 7.3Hz, NCH_2 x 2), 1.4-1.9 (30H, m), 1.04 (12H, t, J = 7.0Hz, CH_3 x 2), 0.91 (4H, m)

Elemental analysis (for $C_{44}H_{70}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 65.57;	H, 9.25;	N, 10.43.
Found (%):	C, 65.32;	H, 9.51;	N, 10.18.

Example 18-1

Trans-1,4-bis[[1-cycloheptyl-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 152-155°C (dihydrochloric acid salt)
MS(FAB): m/e = 711 (M^++1)
IR(KBr) ν MAX: 2931(brs), 1633(s), 1530(s)
NMR(DMSO-d_6) δ: 8.29 (2H, brs, NH x 2), 7.5-7.7 (8H, brs, Ar-H), 3.78 (2H, m, NCH x 2), 3.5-3.7 (8H, m, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.9-2.2 (38H, m)

Elemental analysis (for $C_{44}H_{66}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 64.45;	H, 8.85;	N, 10.25.
Found (%):	C, 64.77;	H, 9.04;	N, 10.43.

Example 19

Trans-1,4-bis[[1-cycloheptyl-3-(6-quinoline)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 181-184°C (dihydrochloric acid salt)
MS(FAB): m/e = 675 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1644(s), 1533(s)
NMR(DMSO-d_6) δ: 9.00 (2H, dd, J = 5.1, 1.5Hz, Ar-H), 8.90 (4H, m, Ar-H), 8.41 (2H, brs, NH x 2), 8.10-8.30 (4H, m, Ar-H), 7.90 (2H, dd, J = 8.4, 5.1Hz, Ar-H), 3.84 (2H, m, NCH x 2), 3.18 (4H, d, J = 7.3Hz, NCH_2 x 2), 1.4-1.9 (30H, m), 0.95 (4H, m)

Elemental analysis (for $C_{42}H_{54}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 65.87;	H, 7.63;	N, 10.97.
Found (%):	C, 66.08;	H, 7.90;	N, 10.60.

Example 20

Trans-1,4-bis[[1-cycloheptyl-3-(1-methylindoli-5-ne)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 150-153°C (dihydrochloric acid salt)
MS(FAB): m/e = 682 ($M+_{+1}$)
IR(KBr) ν MAX: 2919(brs), 1641(s), 1536(s)
NMR(DMSO-d_6) δ: 8.03 (2H, brs, NH x 2), 7.42 (2H, brs, Ar-H), 7.27 (2H, brs, Ar-H), 7.05 (2H, brs, Ar-H), 3.76 (2H, brs, NCH x 2), 2.8-3.2 (14H, m, NCH_3 x 2, NCH_2CH_2 x 2), 1.4-1.8 (30H, m), 0.90 (4H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 63.70;	H, 8.65;	N, 10.61.
Found (%):	C, 63.90;	H, 8.89;	N, 10.40.

Example 21

Trans-1,4-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 172-176°C (maleic acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1630(s), 1521(s)
NMR(DMSO-d_6) δ: 7.67 (2H, brs, NH x 2), 7.22 (4H, d, J = 9.2Hz, Ar-H), 6.71 (4H, d, J = 8.4Hz, Ar-H), 6.19 (2H, s, = CH x 2), 3.74 (2H, m, NCH x 2), 3.03 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.85 (12H, s, $N(CH_3)_2$ x 2), 1.45-1.75 (30H, m), 0.91 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot C_4H_4O_4$)			
Calculated (%):	C, 68.19;	H, 8.58;	N, 10.84.
Found (%):	C, 68.45;	H, 8.91;	N, 11.03.

Example 22

Trans-1,4-bis[[1-cycloheptyl-3-(4-dimethyaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 198-202°C (fumaric acid salt)
MS(FAB): m/e = 658 (M^+)
IR(KBr) ν MAX: 2924(brs), 1626(s), 1520(s)
NMR(DMSO-d_6) δ: 7.61 (2H, brs, NH x 2), 7.18 (4H, brs, Ar-H), 6.62 (4H, brs, Ar-H), 6.56 (2H, s, = CH x 2), 3.76 (2H, m, NCH x 2), 3.02 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.44-1.73 (30H, m), 0.91 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot C_4H_4O_4$)			
Calculated (%):	C, 68.19;	H, 8.58;	N, 10.84.
Found (%):	C, 68.30;	H, 8.70;	N, 10.56.

Example 23

Trans-1,4-bis[[1-cycloheptyl-3-(4-dimethyaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 218-222°C (dioxalic acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2926(brs), 1633(s), 1520(s)
NMR(DMSO-d_6) δ: 7.64 (2H, brs, NH x 2), 7.20 (4H, d, J = 9.2Hz, Ar-H), 6.67 (4H, d, J = 9.2Hz, Ar-H), 3.75 (2H, m, NCH x 2), 3.03 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.82 (12H, s, $N(CH_3)_2$ x 2), 1.44-1.75 (30H, m), 0.91 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2C_2H_2O_4 \cdot H_2O$)			
Calculated (%):	C, 62.71;	H, 7.79;	N, 9.54.
Found (%):	C, 62.51;	H, 8.26;	N, 9.90.

Example 24

Trans-1,4-bis[[1-cycloheptyl-3-(4-dimethyaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 112-117°C (dimethanesulfonic acid salt)
MS(FAB): m/e = 658 (M^+)
IR(KBr) ν MAX: 2929(brs), 1637(s), 1518(s)
NMR(DMSO-d_6) δ: 8.24 (2H, brs, NH x 2), 7.55 (4H, d, J = 9.2Hz, Ar-H), 7.43 (4H, d, J = 9.2Hz, Ar-H), 3.77 (2H, m, NCH x 2), 3.13 (12H, s, $N(CH_3)_2$ x 2), 3.08 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.39 (6H, s, SCH_3 x 2), 1.45-1.75 (30H, m), 0.91 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2CH_4O_3S \cdot 6H_2O$)			
Calculated (%):	C, 52.59;	H, 8.62;	N, 8.76.
Found (%):	C, 52.44;	H, 8.72;	N, 8.65.

Example 25

Trans-1,4-bis[[1-cycloheptyl-3-(4-dimethyaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 142-146°C (di-p-toluenesulfonic acid salt)
MS(FAB): m/e = 658 (M^+)
IR(KBr) ν MAX: 2929(brs), 1637(s), 1517(s)
NMR(DMSO-d_6) δ: 8.21 (2H, brs, NH x 2), 7.52 (8H, m, Ar-H), 7.43 (4H, d, J = 8.8Hz, Ar-H), 7.10 (4H, d, J = 8.8Hz, Ar-H), 3.76 (2H, m, NCH x 2), 3.11 (12H, s, $N(CH_3)_2$ x 2), 3.07 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.28 (6H, Ph-CH_3 x 2), 1.42-1.74 (30H, m), 0.90 (4H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2C_7H_8O_3S \cdot 2H_2O$)			
Calculated (%):	C, 62.40;	H, 7.95;	N, 8.09.
Found (%):	C, 62.64;	H, 8.20;	N, 7.83.

Example 26

Trans-1,4-bis[[1-cyclooctyl-3-(4-dimethyaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 194-196°C (dihydrochloric acid salt) MS(FAB): m/e = 687 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1648(s), 1519(s)
NMR(DMSO-d_6) δ: 8.17 (2H, s, NH x 2), 7.52 (8H, s, Ar-H), 3.78 (2H, s, NCH x 2), 3.0-3.1 (16H, NCH_2 x 2, $N(CH_3)_2$ x 2), 1.4-1.9 (34H, m), 0.8-1.0 (4H, m)

Elemental analysis (for $C_{42}H_{66}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 64.84;	H, 9.07;	N, 10.80.
Found (%):	C, 64.50;	H, 9.00;	N, 10.70.

Example 27

Trans-1,4-bis[[3-(4-dimethyaminophenyl)-1-(2-norbornyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 174-178°C (free form)
MS(FAB): m/e = 655 (M^++1)
IR(KBr) ν MAX: 2954(s), 1625(s), 1590(s), 1519(s)
NMR(DMSO-d_6) δ: 7.66 (2H, s, NH x 2), 7.19 (4H, d, J = 9.0Hz, Ar-H), 6.62 (4H, d, J = 9.0Hz, Ar-H), 3.70 (2H, m, NCH x 2),
3.0-3.4 (4H, m, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 0.8-2.3 (30H, m)

Elemental analysis (for $C_{40}H_{58}N_6O_2 \cdot 3H_2O$)			
Calculated (%):	C, 67.76;	H, 9.10;	N, 11.85.
Found (%):	C, 67.69;	H, 8.86;	N, 11.66.

Example 28

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-(4-methylcyclohexyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 150-153°C (dihydrochloric acid salt)
MS(FAB): m/e = 658 (M^+)
IR(KBr) ν MAX: 2923(brs), 1637(s), 1519(s)
NMR(DMSO-d_6) δ: 8.24 (2H, s, NH x 2), 7.4-7.7 (8H, s, Ar-H), 3.6-3.9 (2H, m, NCH x 2), 3.0-3.2 (16H, br, NCH_2 x 2, $N(CH_3)_2$ x 2), 0.8-1.9 (34H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 62.56;	H, 8.93;	N, 10.94.
Found (%):	C, 62.31;	H, 8.80;	N, 10.90.

Example 28-1

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-(4-methylcyclohexyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 148-155°C (dihydrochloric acid salt)
MS(FAB): m/e = 715 (M^+)
IR(KBr) ν MAX: 2931(brs), 1631(s), 1532(s)
NMR(DMSO-d_6) δ: 8.39 (2H, s, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.4-3.9 (10H, m, NCH x 2, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-1.8 (46H, m)

Elemental analysis (for $C_{44}H_{70}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 64.14;	H, 9.30;	N, 10.20.
Found (%):	C, 64.21;	H, 9.19;	N, 10.16.

Example 28-2

Trans-1,4-bis[[1-(4-methylcyclohexyl)-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 149-155°C (dihydrochloric acid salt)
MS(FAB): m/e = 711 (M^+)
IR(KBr) ν MAX: 2939(brs), 1635(s), 1538(s)
NMR(DMSO-d_6) δ: 8.20 (2H, s, NH x 2), 7.2-7.6 (8H, br, Ar-H), 3.4-3.9 (10H, m, NCH x 2, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-2.2 (42H, m)

Elemental analysis (for $C_{44}H_{66}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 64.45;	H, 8.85;	N, 10.25.
Found (%):	C, 64.23;	H, 8.60;	N, 10.08.

Example 28-3

Trans-1,4-bis[[1-(4-methylcyclohexyl)-3-(4-piperidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 161-165°C (dihydrochloric acid salt)

MS(FAB): m/e = 739 (M^+)
IR(KBr) ν MAX: 2935(brs), 1633(s), 1531(s)
NMR(DMSO-d_6) δ: 8.29 (2H, brs, NH x 2), 7.3-7.7 (8H, br, Ar-H), 3.2-3.9 (10H, m, NCH x 2, $N(CH_2)_2$ x 2), 3.0-3.2 (4H, br, NCH_2 x 2), 0.8-1.8 (46H, m)

Elemental analysis (for $C_{44}H_{66}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 65.15;	H, 9.03;	N, 9.91.
Found (%):	C, 64.95;	H, 8.82;	N, 10.01.

Example 29

Trans-1,4-bis[[1-(2-adamantyl)-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 182-185°C (free form)
MS(FAB): m/e = 735 (M^++1)
IR(KBr) ν MAX: 2908(brs), 1627(s), 1589(s), 1519(s)
NMR(DMSO-d_6) δ: 8.24 (2H, s, NH x 2), 7.19 (4H, d, J = 9.2Hz, Ar-H), 6.63 (4H, d, J = 9.2Hz, Ar-H), 3.64 (2H, s, NCH x 2), 3.15 (4H, br, NCH_2 x 2), 2.80 (12H, s, $N(CH_3)_2$ x 2), 2.23 (4H, m), 1.4-1.9 (30H, m), 0.7-0.9 (4H, m)

Elemental analysis (for $C_{46}H_{66}N_6O_2 \cdot 3H_2O$)			
Calculated (%):	C, 71.65;	H, 9.15;	N, 10.90.
Found (%):	C, 71.69;	H, 9.63;	N, 10.39.

Example 30

Trans-1,4-bis[[1-benzyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 142-144°C (dihydrochloric acid salt)
MS(FAB): m/e = 647 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1646(s), 1519(s)
NMR(DMSO-d_6) δ: 8.55 (2H, s, NH x 2), 7.5-7.7 (8H, brs, Ar-H), 7.2-7.35 (10H, m, Ar-H), 4.59 (4H, brs, Ph-CH_2 x 2), 3.0-3.3 (16H, $N(CH_3)_2$ x 2, NCH_2 x 2), 1.5-1.7 (6H, m), 0.8-1.0 (4H, m)

Elemental analysis (for $C_{40}H_{50}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 66.75;	H, 7.28;	N, 11.68.
Found (%):	C, 66.50;	H, 7.00;	N, 11.40.

Example 31

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-(2-phenetyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 203-205°C (dihydrochloric acid salt)
MS(FAB): m/e = 675 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1664(s), 1533(s)
NMR(DMSO-d_6) δ: 8.34 (2H, s, NH x 2), 7.56 (8H, br, Ar-H), 7.1-7.3 (10H, m, Ar-H), 3.54 (4H, t, J = 7.5Hz, NCH_2 x 2), 3.13 (4H, d, J = 7.0Hz, NCH_2 x 2), 3.06 (12H, $N(CH_3)_2$ x 2), 2.80 (4H, t, J = 7.5Hz, Ph-CH_2 x 2)

Elemental analysis (for $C_{42}H_{54}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 65.87;	H, 7.63;	N, 10.97.
Found (%):	C, 66.06;	H, 7.41;	N, 11.07.

Example 32

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-[2-(1-cyclohexenyl)ethyl]ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 208-210°C (dihydrochloric acid salt)
MS(FAB): m/e = 683 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1637(s), 1519(s)
NMR(DMSO-d_6) δ: 8.42 (2H, brs, NH x 2), 7.5-7.7 (8H, br, Ar-H), 5.40 (2H, brs, = CH x 2), 3.0-3.6 (20H, br, NCH_2 x 2, NCH_2 x 2, $N(CH_3)_2$ x 2), 0.9-2.2 (30H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 64.43;	H, 8.63;	N, 10.73.
Found (%):	C, 64.62;	H, 8.82;	N, 10.79.

Example 33

Trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-furfurylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 195-199°C (free form)
MS(FAB): m/e = 627 (M^++1)
IR(KBr) ν MAX: 2884(brs), 1619(s), 1594(s), 1519(s) NMR(DMSO-d_6) δ: 7.88 (2H, s, NH x 2), 7.53 (2H, s, Ar-H), 7.21 (4H, 6.37 (2H, m, Ar-H), 6.27 (2H, m, Ar-H), 4.51 (4H, s, NH_2 x 2), 3.15 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.82 (12H, s, $N(CH_3)_2$ x 2), 1.5-1.7 (6H, m), 0.8-1.0 (4H, m)

Elemental analysis (for $C_{36}H_{48}N_6O_4$)			
Calculated (%):	C, 68.99;	H, 7.40;	N, 13.41.
Found (%):	C, 68.96;	H, 7.72;	N, 13.85.

Example 34

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-normalheptylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 112-114°C (free form)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1617(s), 1521(s)
NMR(DMSO-d_6) δ: 7.69 (2H, s, NH x 2), 7.21 (4H, d, J = 9.2Hz, Ar-H), 6.62 (4H, d, J = 9.2Hz, Ar-H), 3.1-3.3 (8H, m, NCH_2 x 4), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.77 (2H, brs), 1.2-1.6 (28H, m), 0.86 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{40}H_{68}N_6O_2$)			
Calculated (%):	C, 72.46;	H, 10.03;	N, 12.68.
Found (%):	C, 72.80;	H, 10.24;	N, 12.80.

Example 35

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-normaloctylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 105-107°C (free form)
MS(FAB): m/e = 690 (M^+)
IR(KBr) ν MAX: 2921(brs), 1620(s), 1521(s)
NMR(DMSO-d_6) δ: 7.67 (2H, s, NH x 2), 7.20 (4H, d, J = 9.2Hz, Ar-H), 6.60 (4H, d, J = 9.2Hz, Ar-H), 3.1-3.3 (8H, m, NCH_2 x 4), 2.82 (12H, s, $N(CH_3)_2$ x 2), 1.78 (2H, brs), 1.2-1.6 (32H, m), 0.86 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{42}H_{70}N_6O_2 \cdot 1/2H_2O$)			
Calculated (%):	C, 72.06;	H, 10.22;	N, 12.01.
Found (%):	C, 72.16;	H, 10.59;	N, 11.94.

Example 36

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-normalnonylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 96-98°C (free form)

MS(FAB): m/e = 719 (M^++1)
IR(KBr) ν MAX: 2913(brs), 1619(s), 1519(s)
NMR(DMSO-d_6) δ: 7.71 (2H, s, NH x 2), 7.22 (4H, d, J = 9.0Hz, Ar-H), 6.64 (4H, d, J = 9.0Hz, Ar-H), 3.1-3.3 (8H, m, NCH_2 x 4), 2.82 (12H, s, $N(CH_3)_2$ x 2), 1.77 (2H, brs, CH x 2), 1.2-1.6 (36H, m), 0.85 (6H, t, J = 6.6Hz, CH_3 x 2)

Elemental analysis (for $C_{44}H_{74}N_6O_2 \cdot H_2O$)			
Calculated (%):	C, 71.70;	H, 10.39;	N, 11.40.
Found (%):	C, 71.91;	H, 10.74;	N, 11.29.

Example 37

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-normaldecylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 125-127°C (free form)
MS(FAB): m/e = 747 (M^++1)
IR(KBr) ν MAX: 2915(brs), 1619(s), 1521(s)
NMR(DMSO-d_6) δ: 7.71 (2H, s, NH x 2), 7.22 (4H, d, J = 9.1Hz, Ar-H), 6.61 (4H, d, J = 9.1Hz, Ar-H), 3.1-3.3 (8H, m, NCH_2 x 4), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.77 (2H, brs, CH x 2), 1.2-1.6 (40H, m, CH_2 x 20), 0.85 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{46}H_{78}N_6O_2 \cdot 3H_2O$)			
Calculated (%):	C, 68.96;	H, 10.57;	N, 10.49.
Found (%):	C, 68.79;	H, 10.82;	N, 10.60.

Example 38

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-neopentylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 178-181°C (dihydrochloric acid salt)
MS(FAB): m/e = 606 (M^+)
IR(KBr) ν MAX: 2933(brs), 1648(s), 1519(s)
NMR(DMSO-d_6) δ: 8.52 (2H, s, NH x 2), 7.5-7.6 (8H, m, ArH x 2), 3.39 (4H, d, J = 7.0Hz, NCH_2 x 2), 3.20 (4H, NCH_2 x 2), 3.05 (12H, s), 1.82 (2H, brs), 1.1-1.3 (8H, m), 0.86 (18H, s, $(CH_3)_3$ x 2)

Elemental analysis (for $C_{36}H_{53}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 60.40;	H, 9.01;	N, 11.74.
Found (%):	C, 60.09;	H, 9.17;	N, 11.54.

Example 39

Cis-1,4-bis[1-cyclohexylmethyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.

mp: 172-175°C (dihydrochloric acid salt)

MS(FAB): m/e = 659 (M^++1)

IR(KBr) ν MAX: 2925(brs), 1643(s), 1517(s)

NMR(DMSO-d_6) δ: 8.40 (2H, s, NH x 2), 7.4-7.7 (8H, s, Ar-H), 3.30 (4H, brs, NCH_2 x 2), 3.17 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 0.8-0.9 (32H, m)

Elemental analysis (for $C_{40}H_{82}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 62.56;	H, 8.93;	N, 10.94.
Found (%):	C, 62.28;	H, 8.75;	N, 11.27.

Example 40

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-(4-heptyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.

mp: 180-183°C (free form)

MS(FAB): m/e = 663 (M^++1)

IR(KBr) ν MAX: 3453(brs), 1620(s), 1592(s), 1519(s)

NMR(DMSO-d_6) δ: 7.58 (2H, s, NH x 2), 7.19 (4H, d, J = 8.8Hz, Ar-H), 6.62 (4H, d, J = 8.8Hz, Ar-H), 3.87 (2H, m, NCH x 2), 3.07 (4H, d, J = 7.0Hz, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.2-1.8 (26H, m), 0.87 (12H, t, J = 7.0Hz, CH_3 x 4)

Elemental analysis (for $C_{40}H_{66}N_6O_2$)			
Calculated (%):	C, 72.46;	H, 10.03;	N, 12.68.
Found (%):	C, 72.83;	H, 10.49;	N, 12.64.

Example 41

Cis-1,4-bis[[1-cyclopentyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.

mp: 162-165°C (dihydrochloric acid salt)

MS(FAB): m/e = 603 (M^++1)

IR(KBr) ν MAX: 2917(brs), 1631(s), 1517(s)

NMR(DMSO-d_6) δ: 8.37 (2H, s, NH x 2), 7.4-7.6 (8H, brs, Ar-H), 4.11 (2H, m, NCH x 2), 3.23 (4H, br, NCH_2 x 2), 3.06 (12H, brs, $N(CH_3)_2$ x 2), 1.3-1.8 (26H, m)

Elemental analysis (for $C_{36}H_{54}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 60.75;	H, 8.50;	N, 11.81.
Found (%):	C, 60.89;	H, 8.44;	N, 11.50.

Example 42

Cis-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 145-147°C (dihydrochloric acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2933(brs), 1635(s), 1517(s)
NMR(DMSO-d_6) δ: 8.39 (2H, s, NH x 2), 7.4-7.7 (8H, brs, Ar-H), 3.77 (2H, brs, NCH x 2), 3.22 (4H, brs, NCH_2 x 2), 3.06 (12H, brs, $N(CH_3)_2$ x 2), 1.0-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 61.69;	H, 8.72;	N, 11.36.
Found (%):	C, 61.70;	H, 8.70;	N, 10.90.

Example 43

Cis-1,4-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 160-163°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1656(s), 1637(s), 1515(s)
NMR(DMSO-d_6) δ: 8.36 (2H, s, NH x 2), 7.4-7.7 (8H, m, Ar-H), 3.73 (2H, m, NCH x 2), 3.23 (4H, d, J = 7.0Hz, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.3-1.9 (34H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 5/2H_2O$)			
Calculated (%):	C, 61.84;	H, 8.95;	N, 10.82.
Found (%):	C, 61.96;	H, 8.65;	N, 10.94.

Example 44

Cis-1,4-bis[[1-cyclooctyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 197-200°C (dihydrochloric acid salt)

MS(FAB): m/e = 606 (M^+)
IR(KBr) ν MAX: 2927(brs), 1643(s), 1523(s)
NMR(DMSO-d_6) δ: 8.10 (2H, brs, NH x 2), 7.2-7.6 (8H, s, Ar-H), 3.72 (2H, m, NCH x 2), 3.20 (4H, m), 3.01 (12H, s, $N(CH_3)_2$ x 2), 1.3-2.0 (38H, m)

Elemental analysis (for $C_{42}H_{66}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 66.38;	H, 9.02;	N, 11.06.
Found (%):	C, 66.25;	H, 9.48;	N, 10.97.

Example 45

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-(2-norbornyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 188-191°C (free form)
MS(FAB): m/e = 655 (M^++1)
IR(KBr) ν MAX: 2942(brs), 1631(s), 1517(s)
NMR(DMSO-d_6) δ: 7.87 (2H, t, J = 9.0Hz, NH x 2), 7.20 (4H, d, J = 9.2Hz, Ar-H), 6.62 (4H, d, J = 9.2Hz, Ar-H), 2.9-3.7 (6H, m, NCH_2 x 2, NCH x 2), 2.80 (12H, s, $N(CH_3)_2$ x 2), 0.8-2.4 (30H, m)

Elemental analysis (for $C_{40}H_{58}N_6O_2 \cdot H_2O$)			
Calculated (%):	C, 71.39;	H, 8.99;	N, 12.49.
Found (%):	C, 71.37;	H, 8.91;	N, 12.04.

Example 46

Cis-1,4-bis[[1-(2-adamantyl)-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 251-255°C (dihydrochloric acid salt)
MS(FAB): m/e = 735 (M^++1)
IR(KBr) ν MAX: 2910(brs), 1708(s), 1560(s), 1515(s) NMR(DMSO-d_6) δ: 8.59 (2H, brs, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.24 (2H, brs, NCH x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 2.88 (4H, brs, NCH_2 x 2), 1.4-2.8 (38H, m)

Elemental analysis (for $C_{46}H_{66}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 64.09;	H, 8.65;	N, 9.75.
Found (%):	C, 63.75;	H, 8.76;	N, 9.78.

Example 47

Cis-1,4-bis[1-benzyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 155-157°C (dihydrochloric acid salt)
MS(FAB): m/e = 647 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1641(s), 1517(s)
NMR(DMSO-d_6) δ: 8.60 (2H, s, NH x 2), 7.2-7.7 (8H, br, Ar-H), 4.60 (4H, br, Ph-CH_2 x 2), 3.31 (4H, br, NCH_2 x 2), 3.05 (12H, brs, $N(CH_3)_2$ x 2), 1.83 (2H, br), 1.38 (8H, m)

Elemental analysis (for $C_{40}H_{50}N_8O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 63.57;	H, 7.47;	N, 11.12.
Found (%):	C, 63.35;	H, 7.70;	N, 10.91.

Example 48

Cis-1,4-bis[[3-(4-dimethylaminophenyl)-1-(2-phenetyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 153-155°C (free form)
MS(FAB): m/e = 675 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1610(s), 1521(s)
NMR(DMSO-d_6) δ: 7.75 (2H, s, NH x 2), 7.1-7.4 (14H, m, Ar-H), 6.62 (4H, d, J = 8.8Hz, Ar-H), 3.50 (4H, m, NCH_2 x 2), 3.1-3.2 (4H, m, NCH_2 x 2), 2.7-2.9 (16H, m, $N(CH_3)_2$ x 2, $ArCH_2$ x 2), 1.76 (2H, brs), 1.36 (8H, brs)

Elemental analysis (for $C_{42}H_{54}N_8O_2 \cdot 2H_2O$)			
Calculated (%):	C, 72.80;	H, 8.15;	N, 12.13.
Found (%):	C, 72.45;	H, 8.37;	N, 12.12.

Example 49

Cis-1,4-bis[[1-[2-(1-cyclohexenyl)ethyl]-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 152-155°C (free form)
MS(FAB): m/e = 683 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1612(s), 1519(s)
NMR(DMSO-d_6) δ: 7.71 (2H, s, NH x 2), 7.21 (4H, d, J = 9.0Hz, Ar-H), 6.62 (4H, d, J = 9.0Hz, Ar-H), 5.41 (2H, s, =CH x 2),
3.35 (4H, t, J = 7.3Hz, NCH_2 x 2), 3.22 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.11 (4H, t, J = 7.3Hz, CH_2 x 2), 1.3-2.6 (26H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_2$)			
Calculated (%):	C, 73.86;	H, 9.15;	N, 12.31.
Found (%):	C, 73.76;	H, 9.27;	N, 12.32.

Example 50

Cis-1,4-bis[[3-[4-dimethylaminophenyl)-1-furfurylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 129-132°C (free form)
MS(FAB): m/e = 627 (M^++1)
IR(KBr) ν MAX: 2911(brs), 1635(s), 1612(s), 1519(s)
NMR(DMSO-d_6) δ: 7.91 (2H, d, NH x 2), 7.55 (4H, d, J = 1.8Hz, Ar-H), 7.22 (4H, d, J = 9.0Hz, Ar-H), 6.63 (4H, d, J = 9.0Hz, Ar-H), 6.38 (2H, m, Ar-H), 6.28 (2H, d, J = 3.3Hz, Ar-H), 4.52 (4H, s, NCH_2 x 2), 3.25 (4H, d, J = 7.3Hz, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.81 (2H, brs), 1.37 (8H, brs)

Elemental analysis (for $C_{36}H_{48}N_6O_2$)			
Calculated (%):	C, 68.99;	H, 7.40;	N, 13.41.
Found (%):	C, 68.71;	H, 7.63;	N, 13.72.

Example 51

Trans-1,3-bis[[3-[4-dimethylaminophenyl)-1-normalpentylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 124-127°C (free form)
MS(FAB): m/e = 607 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1631(s), 1587(s), 1519(s)
NMR(DMSO-d_6) δ: 7.67 (2H, s, NH x 2), 7.19 (4H, d, J = 9.0Hz, Ar-H), 6.59 (4H, d, J = 9.0Hz, Ar-H), 3.1-3.3 (8H, m, NCH_2 x 2), 2.79 (12H, s, $N(CH_3)_2$ x 2), 1.96 (2H, brs, CH_2 x 2), 1.1-1.5 (20H, m), 0.84 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{36}H_{58}N_6O_2 \cdot H_2O$)			
Calculated (%):	C, 69.19;	H, 9.68;	N, 13.45.
Found (%):	C, 68.85;	H, 10.05;	N, 13.28.

Example 52

Trans-1,3-bis[[3-[4-dimethylaminophenyl)-1-normalhexylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 144-150°C (dihydrochloric acid salt)
MS(FAB): m/e = 635 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1648(s), 1519(s)
NMR(DMSO-d_6) δ: 8.38 (2H, s, NH x 2), 7.5-7.65 (8H, m, Ar-H), 3.1-3.4 (8H, m, NCH_2 x 4), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.97 (2H, brs), 1.1-1.6 (24H, m), 0.84 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{38}H_{62}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 62.88;	H, 9.16;	N, 11.58.
Found (%):	C, 63.04;	H, 9.26;	N, 11.70.

Example 53

Trans-1,3-bis[[3-[4-dimethylaminophenyl)-1-normalheptylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 121-126°C (dihydrochloric acid salt)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1643(s), 1517(s)
NMR(DMSO-d_6) δ: 8.31 (2H, s, NH x 2), 7.4-7.7 (8H, br, Ar-H), 3.0-3.4 (20H, m, NCH_2 x 4, $N(CH_3)_2$ x 2), 1.98 (2H, brs), 1.2-1.6 (28H, m), 0.84 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{40}H_{66}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 60.82;	H, 9.44;	N, 10.64.
Found (%):	C, 60.63;	H, 9.63;	N, 10.61.

Example 54

Trans-1,3-bis[[3-[4-dimethylaminophenyl)-1-normaloctylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 115-119°C (dihydrochloric acid salt)
MS(FAB): m/e = 691 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1641(s), 1519(s)
NMR(DMSO-d_6) δ: 8.34 (2H, brs, NH x 2), 7.5-7.6 (8H, br, Ar-H), 3.1-3.4 (8H, m, NCH_2 x 4), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.96 (2H, m), 1.46 (6H, m), 1.2-1.4 (26H, m), 0.84 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{42}H_{70}N_6O_2 \cdot 2HCl \cdot 1/2H_2O$)			
Calculated (%):	C, 65.56;	H, 10.20;	N, 10.50.
Found (%):	C, 65.26;	H, 9.90;	N, 10.87.

Example 55

Trans-1,3-bis[[3-[4-dimethylaminophenyl)-1-normalnonylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 116-120°C (dihydrochloric acid salt)
MS(FAB): m/e = 719 (M^++1)
IR(KBr) ν MAX: 2908(brs), 1656(s), 1639(s), 1517(s)
NMR(DMSO-d_6) δ: 8.38 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.1-3.4 (8H, m, NCH_2 x 4), 3.07 (12H, s, $N(CH_3)_2$ x 2), 1.98 (2H, brs), 1.2-1.6 (36H, m), 0.85 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{44}H_{74}N_6O_2 \cdot 2HCl \cdot 1/2H_2O$)			
Calculated (%):	C, 65.98;	H, 9.69;	N, 10.49.
Found (%):	C, 65.70;	H, 9.54;	N, 9.92.

Example 56

Trans-1,3-bis[[3-(4-dimethylaminophenyl)-1-normaldecylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 115-117°C (dihydrochloric acid salt)
MS(FAB): m/e = 747 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1652(s), 1517(s)
NMR(DMSO-d_6) δ: 8.35 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.1-3.4 (8H, m, NCH_2 x 4), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.96 (2H, m), 1.2-1.6 (40H, m), 0.84 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{46}H_{78}N_6O_2 \cdot 2HCl \cdot 5/2H_2O$)			
Calculated (%):	C, 63.86;	H, 9.90;	N, 9.71.
Found (%):	C, 63.64;	H, 9.67;	N, 9.66.

Example 57

Trans-1,3-bis[[1-cyclohexylmethyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 161-164°C (free form)

MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2850(brs), 1629(s), 1590(s), 1519(s)
NMR(DMSO-d_6) δ: 7.62 (2H, s, NH x 2), 7.15 (4H, d, J = 9.0Hz, Ar-H), 6.55 (4H, d, J = 9.0Hz, Ar-H), 3.0-3.3 (8H, m, NCH_2 x 2), 2.74 (12H, s, $N(CH_3)_2$ x 2), 1.92 (2H, brs), 0.7-1.6 (30H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 1/2H_2O$)			
Calculated (%):	C, 71.92;	H, 9.51;	N, 12.58.
Found (%):	C, 71.74;	H, 10.04;	N, 12.33.

Example 58

Trans-1,3-bis[[3-(4-dimethylaminophenyl)-1-(4-normalheptyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 122-126°C (dihydrochloric acid salt)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2917(brs), 1631(s), 1519(s)
NMR(DMSO-d_6) δ: 8.26 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.90 (2H, m, NCH x 2), 2.9-3.2 (4H, m, NCH_2 x 4), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.86 (2H, brs, CH x 2), 1.2-1.6 (24H, m), 0.8-0.9 (12H, m, CH_3 x 4)

Elemental analysis (for $C_{40}H_{66}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 60.82;	H, 9.44;	N, 10.64.
Found (%):	C, 60.95;	H, 9.34;	N, 10.39.

Example 59

Trans-1,3-bis[[1-cyclopentyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 142-147°C (free form)
MS(FAB): m/e = 603 (M^++1)
IR(KBr) ν MAX: 2938(brs), 1639(s), 1617(s), 1519(s)
NMR(DMSO-d_6) δ: 7.69 (2H, s, NH x 2), 7.19 (4H, d, J = 9.2Hz, Ar-H), 6.61 (4H, d, J = 9.2Hz, Ar-H), 4.06 (2H, m, NCH x 2), 3.0-3.2 (4H, m, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.2-2.0 (26H, m)

Elemental analysis (for $C_{36}H_{54}N_6O_2$)			
Calculated (%):	C, 71.72;	H, 9.03;	N, 13.94.
Found (%):	C, 71.57;	H, 9.55;	N, 14.03.

Example 60

Trans-1,3-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 153-159°C (dihydrochloric acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1639(s), 1517(s)
NMR(DMSO-d_6) δ: 8.38 (2H, s, NH x 2), 7.56 (8H, s, Ar-H), 3.78 (2H, brs, NCH x 2), 3.0-3.3 (16H, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.1-2.0 (28H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 60.22;	H, 8.78;	N, 11.09.
Found (%):	C, 59.83;	H, 8.56;	N, 11.29.

Example 61

Trans-1,3-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 109-114°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1643(s), 1592(s), 1516(s)
NMR(DMSO-d_6) δ: 8.36 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.74 (2H, m, NCH x 2), 2.9-3.2 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.0-2.0 (34H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 62.56;	H, 8.93;	N, 10.94.
Found (%):	C, 62.30;	H, 8.83;	N, 10.93.

Example 62

Trans-1,3-bis[[3-(4-dimethylaminophenyl)-1-(2-norbornyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 126-129°C (free form)
MS(FAB): m/e = 655 (M^++1)
IR(KBr) ν MAX: 2933(brs), 1629(s), 1594(s), 1519(s)
NMR(DMSO-d_6) δ: 7.68 (2H, s, NH x 2), 7.19 (4H, m, Ar-H), 6.62 (4H, m, Ar-H), 3.67 (2H, m, NCH x 2), 2.9-3.5 (4H, m, NCH_2 x 2), 2.80 (12H, s, $N(CH_3)_2$ x 2), 1.0-2.4 (30H, m)

Elemental analysis (for $C_{40}H_{58}N_6O_2 \cdot H_2O$)			
Calculated (%):	C, 71.39;	H, 8.99;	N, 12.49.
Found (%):	C, 71.41;	H, 9.38;	N, 12.48.

Example 63

Trans-1,3-bis[[3-(4-dimethylaminophenyl)-1-(4-methylcyclohexyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 106-110°C (free form)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2918(brs), 1629(s), 1592(s), 1517(s)
NMR(DMSO-d_6) δ: 7.69 (2H, s, NH x 2), 7.19 (4H, d, J = 9.0Hz, Ar-H), 6.61 (4H, d, J = 9.0Hz, Ar-H), 3.6-3.8 (2H, m, NCH x 2), 3.0-3.2 (4H, m, NCH_2 x 4), 2.81 (12H, s, $N(CH_3)_2$ x 2), 0.8-2.0 (22H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 5/2H_2O$)			
Calculated (%):	C, 68.24;	H, 9.59;	N, 11.94.
Found (%):	C, 68.01;	H, 9.60;	N, 11.49.

Example 64

Trans-1,3-bis[[3-(4-dimethylaminophenyl)-1-benzylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 158-163°C (free form)
MS(FAB): m/e = 646 (M^+)
IR(KBr) ν MAX: 3461(brs), 1633(s), 1458(s)
NMR(DMSO-d_6) δ: 8.66 (2H, s, NH x 2), 7.5-7.7 (8H, brs, Ar-H), 7.1-7.35 (10H, m, Ar-H), 4.61 (4H, brs, NCH_2Ph x 2), 3.18 (4H, NCH_2 x 2), 3.04 (12H, $N(CH_3)_2$ x 2), 2.03 (2H, brs), 1.1-1.6 (8H, m)

Elemental analysis (for $C_{40}H_{50}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 63.48;	H, 7.51;	N, 10.97.
Found (%):	C, 63.57;	H, 7.47;	N, 11.12.

Example 65

Trans-1,3-bis[[3-(4-dimethylaminophenyl)-1-(2-phenetyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 130-135°C (free form)

MS(FAB): m/e = 675 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1633(s), 1592(s), 1523(s)
NMR(DMSO-d_6) δ: 7.33 (2H, s, NH x 2), 7.1-7.3 (14H, m, Ar-H), 6.61 (4H, d, J = 8.8Hz, Ar-H), 3.48 (4H, m, NCH_2 x 2), 3.13 (4H, m, J = 7.7Hz, NCH_2 x 2), 2.7-2.9 (16H, m, $N(CH_3)_2$ x 2, $PhCH_2$ x 2), 1.95 (2H, brs), 1.1-1.5 (8H, m)

Elemental analysis (for $C_{42}H_{54}N_6O_2$)			
Calculated (%):	C, 74.74;	H, 8.06;	N, 12.45.
Found (%):	C, 74.60;	H, 8.36;	N, 12.37.

Example 66

Trans-1,3-bis[[1-[2-(1-cyclohexenyl)ethyl]-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 129-131°C (free form)
MS(FAB): m/e = 683 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1641(s), 1594(s), 1529(s)
NMR(DMSO-d_6) δ: 7.72 (2H, s, NH x 2), 7.23 (4H, d, J = 8.8Hz, Ar-H), 6.64 (4H, d, J = 8.8Hz, Ar-H), 5.42 (2H, s, = CH x 2), 3.37 (4H, m, NCH_2 x 2), 3.1-3.2 (4H, m, NCH_2 x 2), 2.83 (12H, s, $N(CH_3)_2$ x 2), 2.11 (4H, m, = C-CH_2 x 2), 1.95 (10H, m), 1.2-1.7 (16H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_2$)			
Calculated (%):	C, 73.86;	H, 9.15;	N, 12.31.
Found (%):	C, 73.77;	H, 9.48;	N, 12.10.

Example 67

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-normalpentylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 172-176°C (dihydrochloric acid salt)
MS(FAB): m/e = 607 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1650(s), 1519(s)
NMR(DMSO-d_6) δ: 8.26 (2H, brs, NH x 2), 7.4-7.6 (8H, m, Ar-H), 3.28 (4H, d, J = 7.0Hz, NCH_2 x 2), 3.17 (4H, NCH_2 x 2), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.1-1.8 (20H, m), 0.6-1.0 (8H, m)

Elemental analysis (for $C_{36}H_{58}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 62.77;	H, 8.93;	N, 12.20.
Found (%):	C, 62.66;	H, 9.42;	N, 12.46.

Example 68

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-normalhexylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 121-125°C (dihydrochloric acid salt)
MS(FAB): m/e = 635 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1650(s), 1521(s)
NMR(DMSO-d_6) δ: 8.32 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.10-3.35 (8H, m, NCH_2 x 4), 3.06 (12H, s, $N(CH_3)_2$ x 2), 0.6-1.8 (32H, m)

Elemental analysis (for $C_{38}H_{62}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 63.67;	H, 9.14;	N, 11.73.
Found (%):	C, 63.78;	H, 9.06;	N, 11.77.

Example 69

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-normalheptylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 124-127°C (dihydrochloric acid salt)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1650(s), 1521(s)
NMR(DMSO-d_6) δ: 8.35 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.10-3.35 (8H, m, NCH_2 x 4), 3.07 (12H, m, $N(CH_3)_2$ x 2), 0.6-1.8 (36H, m)

Elemental analysis (for $C_{40}H_{66}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 63.72;	H, 9.36;	N, 11.15.
Found (%):	C, 63.43;	H, 9.05;	N, 11.44.

Example 70

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-normaloctylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 118-121°C (dihydrochloric acid salt)
MS(FAB): m/e = 690 (M^+)
IR(KBr) ν MAX: 2927(brs), 1643(s), 1519(s)
NMR(DMSO-d_6) δ: 8.32 (2H, brs, NH x 2), 7.5-7.6 (8H, br, Ar-H), 3.28 (4H, m, NCH_2 x 2), 3.17 (4H, m, NCH_2 x 2), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.4-1.8 (8H, m), 1.24 (24H, brs, CH_2 x 6 x 2), 0.6-0.9 (8H, m)

Elemental analysis (for $C_{42}H_{70}N_6O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 63.78;	H, 9.86;	N, 10.63.
Found (%):	C, 63.68;	H, 9.79;	N, 10.83.

Example 71

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-normalnonylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 132-133°C (dihydrochloric acid salt)
MS(FAB): m/e = 719 (M^++1)
IR(KBr) ν MAX: 2925(brs), 1646(s), 1521(s)
NMR(DMSO-d_6) δ: 8.34 (2H, s, NH x 2), 7.5-7.65 (8H, br, Ar-H), 3.15-3.35 (8H, m NCH_2 x 4), 3.06 (12H, s, $N(CH_3)_2$ x 2), 0.55-1.8 (44H, m)

Elemental analysis (for $C_{44}H_{74}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 65.98;	H, 9.69;	N, 10.49.
Found (%):	C, 65.77;	H, 10.19;	N, 10.35.

Example 72

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-normaldecylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 165-170°C (dihydrochloric acid salt)
MS(FAB): m/e = 747 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1650(s), 1519(s)
NMR(DMSO-d_6) δ: 8.28 (2H, brs, NH x 2), 7.4-7.6 (8H, br, Ar-H), 3.28 (4H, br, NCH_2 x 2), 3.17 (4H, m, NCH_2 x 2), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.1-1.8 (40H, m), 0.6-0.9 (8H, m)

Elemental analysis (for $C_{46}H_{78}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 66.64;	H, 9.85;	N, 10.14.
Found (%):	C, 66.60;	H, 10.14;	N, 10.34.

Example 73

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-neopentylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 171-173°C (dihydrochloric acid salt)

MS(FAB): m/e = 607 (M^++1)
IR(KBr) ν MAX: 2931(brs), 1644(s), 1542(s)
NMR(DMSO-d_6) δ: 8.50 (2H, s, NH x 2), 7.58 (8H, s, Ar-H), 3.10-3.35 (8H, m, NCH_2 x 4), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.68-1.75 (6H, m), 0.55-1.2 (20H, m)

Elemental analysis (for $C_{36}H_{58}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 61.96;	H, 8.96;	N, 12.04.
Found (%):	C, 61.69;	H, 8.74;	N, 12.22.

Example 74

Cis-1,3-bis[[1-cyclohexylmethyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 136-140°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1635(s), 1527(s)
NMR(DMSO-d_6) δ: 8.41 (2H, s, NH x 2), 7.55-7.65 (8H, brs, Ar-H), 3.1-3.3 (8H, br, NCH_2 x 4), 3.07 (12H, s, $N(CH_3)_2$ x 2), 0.6-1.8 (32H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 62.56;	H, 8.93;	N, 10.94.
Found (%):	C, 62.43;	H, 8.83;	N, 10.88.

Example 75

Cis-1,3-bis[[1-isopropyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 139-141°C (dihydrochloric acid salt)
MS(FAB): m/e = 551 (M^++1)
IR(KBr) ν MAX: 2919(brs), 1644(s), 1523(s)
NMR(DMSO-d_6) δ: 8.35 (2H, s, NH x 2), 7.56 (8H, br, Ar-H), 4.18 (2H, m, NCH x 2), 3.0-3.15 (16H, m, NCH_2 x 2, $N(CH_3)_2$ x 2), 1.55-1.8 (6H, m), 0.6-1.2 (22H, m)

Elemental analysis (for $C_{32}H_{50}N_6O_2 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 59.89;	H, 8.48;	N, 13.10.
Found (%):	C, 59.50;	H, 8.44;	N, 13.30.

Example 76

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-(3-pentyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 157-160°C (free form)
MS(FAB): m/e = 607 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1629(s), 1592(s), 1521(s) NMR(DMSO-d_6) δ: 7.62 (2H, s, NH x 2), 7.19 (4H, d, J = 9.2Hz, Ar-H), 6.61 (4H, d, J = 9.2Hz, Ar-H), 3.67 (2H, m, NCH x 2), 2.97 (4H, m, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.4-1.9 (18H, m), 0.83 (12H, m, CH_3 x 4)

Elemental analysis (for $C_{36}H_{58}N_6O_2$)			
Calculated (%):	C, 71.25;	H, 9.63;	N, 13.85.
Found (%):	C, 71.76;	H, 9.97;	N, 13.73.

Example 77

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-(4-heptyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 130-140°C (dihydrochloric acid salt)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2960(brs), 1633(s), 1519(s)
NMR(DMSO-d_6) δ: 8.25 (2H, s, NH x 2), 7.54 (8H, m, Ar-H), 3.93 (2H, m, NCH x 2), 2.9-3.1 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 0.6-1.8 (38H, m)

Elemental analysis (for $C_{40}H_{66}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 60.82;	H, 9.44;	N, 10.64.
Found (%):	C, 60.55;	H, 9.70;	N, 10.87.

Example 78

Cis-1,3-bis[[1-cyclopentyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 138-140°C (dihydrochloric acid salt)
MS(FAB): m/e = 602 (M^+)
IR(KBr) ν MAX: 2919(brs), 1648(s), 1519(s)
NMR(DMSO-d_6) δ: 8.37 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 4.16 (2H, m, NCH x 2), 3.05-3.2 (16H, m, NCH_2 x 2, $N(CH_3)_2$ x 2), 1.4-1.8 (22H, m), 0.6-1.2 (4H, m)

Elemental analysis (for $C_{36}H_{54}N_6O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 61.52;	H, 8.46;	N, 11.96.
Found (%):	C, 61.70;	H, 8.28;	N, 12.48.

Example 79

Cis-1,3-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 145-146°C (dihydrochloric acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1648(s), 1523(s)
NMR(DMSO-d_6) δ: 8.35 (2H, s, NH x 2), 7.5-7.6 (8H, brs, Ar-H), 3.79 (2H, br, NCH x 2), 3.0-3.15 (16H, m), 0.55-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 62.45;	H, 8.69;	N, 11.50.
Found (%):	C, 62.05;	H, 8.67;	N, 11.61.

Example 80

Cis-1,3-bis[[1-cyclohexyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 174-178°C (dihydrochloric acid salt)
MS(FAB): m/e = 711 (M^++1)
IR(KBr) ν MAX: 2935(brs), 1652(s), 1515(s)
NMR(DMSO-d_6) δ: 8.36 (2H, s, NH x 2), 7.5-7.8 (8H, m, Ar-H), 3.79 (2H, br, NCH x 2), 3.2-3.5 (8H, m, $N(CH_2)_2$ x 2), 3.08 (4H, NCH_2 x 2), 0.5-1.8 (42H, m)

Elemental analysis (for $C_{44}H_{66}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 67.41;	H, 8.74;	N, 10.72.
Found (%):	C, 67.20;	H, 9.12;	N, 10.60.

Example 81

Cis-1,3-bis[[1-cyclohexyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 170-172°C (dihydrochloric acid salt)

MS(FAB): m/e = 687 (M^++1)
IR(KBr) ν MAX: 2940(brs), 1646(s), 1515(s)
NMR(DMSO-d_6) δ: 8.39 (2H, s, NH x 2), 7.5-7.8 (8H, m, Ar-H), 3.79 (2H, m, NCH x 2), 3.4-3.6 (8H, m, $N(CH_2)_2$ x 2), 3.08 (4H, NCH_2 x 2), 0.5-1.8 (42H, m)

Elemental analysis (for $C_{42}H_{68}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 61.97;	H, 9.16;	N, 10.33.
Found (%):	C, 61.60;	H, 8.89;	N, 10.44.

Example 82

Cis-1,3-bis[[1-cyclohexyl-3-(1-methylindoli-5-ne)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 154-156°C (dihydrochloric acid salt)
MS(FAB): m/e = 654 (M^++1)
IR(KBr) ν MAX: 2921(s), 1644(s), 1496(s)
NMR(DMSO-d_6) δ: 8.22 (2H, s, NH x 2), 7.1-7.6 (6H, m, Ar-H), 3.6-3.9 (6H, m, NCH x 2, NCH_2CH_2 x 2), 2.9-3.2 (14H, m, NCH_2 x 2, NCH_2CH_2 x 2, NCH_3 x 2), 0.5-1.8 (30H, m)

Elemental analysis (for $C_{40}H_{58}N_6O_2 \cdot 2HCl \cdot 5/2H_2O$)			
Calculated (%):	C, 62.16;	H, 8.48;	N, 10.87.
Found (%):	C, 62.26;	H, 8.25;	N, 10.98.

Example 83

Cis-1,3-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 166-168°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2927(s), 1646(s), 1593(s), 1524(s)
NMR(DMSO-d_6) δ: 8.36 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.76 (2H, m, NCH x 2), 3.0-3.2 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 0.5-1.8 (34H, m, CH_2 x 17)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 3/2H_2O$)			
Calculated (%):	C, 63.31;	H, 8.63;	N, 11.07.
Found (%):	C, 62.25;	H, 8.75;	N, 11.10.

Example 84

Cis-1,3-bis[[1-cyclooctyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 147-149°C (dihydrochloric acid salt)
MS(FAB): m/e = 687 (M^++1)
IR(KBr) ν MAX: 2921(s), 1643(s), 1521(s)
NMR(DMSO-d_6) δ: 8.23 (2H, s, NH x 2), 7.54 (8H, s, Ar-H), 3.78 (2H, m, NCH x 2), 3.0-3.2 (16H, NCH_2 x 2, $N(CH_3)_2$ x 2), 0.6-1.9 (38H, m)

Elemental analysis (for $C_{42}H_{66}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 65.60;	H, 9.04;	N, 10.93.
Found (%):	C, 65.49;	H, 9.10;	N, 11.36.

Example 85

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-(2-norbornyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 110-115°C (free form)
MS(FAB): m/e = 655 (M^++1)
IR(KBr) ν MAX: 2950(s), 1635(s), 1627(s), 1519(s)
NMR(DMSO-d_6) δ: 7.67 (2H, brs, NH x 2), 7.20 (4H, m, Ar-H), 6.62 (4H, m, Ar-H), 3.72 (2H, m, NCH x 2), 2.9-3.3 (4H, m, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 2.27 (2H, brs), 2.19 (2H, brs), 0.7-1.9 (26H, m)

Elemental analysis (for $C_{40}H_{53}N_6O_2 \cdot 2H_2O$)			
Calculated (%):	C, 69.53;	H, 9.04;	N, 12.16.
Found (%):	C, 69.72;	H, 9.20;	N, 11.72.

Example 86

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-benzylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 129-133°C (dihydrochloric acid salt)
MS(FAB): m/e = 646 (M^+)
IR(KBr) ν MAX: 2925(brs), 1648(s), 1521(s)
NMR(DMSO-d_6) δ: 8.55 (2H, s, NH x 2), 7.50-7.65 (6H, m, Ar-H), 7.15-7.35 (8H, m, Ar-H), 4.53-4.65 (4H, m, $PhCH_2$ x 2), 3.18 (4H, t, J = 7.3Hz, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.5-1.8 (6H, m), 0.6-1.2 (4H, m)

Elemental analysis (for $C_{40}H_{50}N_6O_2 \cdot 2HCl \cdot 1/2H_2O$)			
Calculated (%):	C, 65.92;	H, 7.33;	N, 11.53.
Found (%):	C, 65.92;	H, 7.66;	N, 11.20.

Example 87

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-(2-phenetyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 167-171°C (dihydrochloric acid salt)
MS(FAB): m/e = 675 (M^++1)
IR(KBr) ν MAX: 2925(s), 1648(s), 1521(s)
NMR(DMSO-d_6) δ: 8.34 (2H, s, NH x 2), 7.5-7.6 (8H, brs, Ar-H), 7.1-7.3 (10H, m, Ar-H), 3.54 (4H, m, N-CH_2CH_2Ph x 2), 3.13 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 2.79 (4H, t, J = 7.5Hz, $PhCH_2$ x 2), 1.5-1.8 (6H, m), 0.55-1.2 (4H, m)

Elemental analysis (for $C_{42}H_{54}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 66.65;	H, 7.59;	N, 11.10.
Found (%):	C, 66.44;	H, 8.06;	N, 11.49.

Example 88

Cis-1,3-bis[[1-[2-(1-cyclohexenyl)ethyl]-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 80-83°C (free form)
MS(FAB): m/e = 683 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1633(s), 1590(s), 1517(s)
NMR(DMSO-d_6) δ: 7.73 (2H, s, NH x 2), 7.24 (4H, d, J = 8.8Hz, Ar-H), 6.66 (4H, d, J = 8.8Hz, Ar-H), 5.44 (2H, s, = CH x 2), 3.38 (4H, m, NCH_2 x 2), 3.17 (4H, m, NCH_2 x 2), 2.85 (12H, s, $N(CH_3)_2$ x 2), 2.13 (4H, m, = C-CH_2 x 2), 0.6-2.1 (26H, m)

Elemental analysis (for $C_{42}H_{62}N_6O_2$)			
Calculated (%):	C, 73.86;	H, 9.15;	N, 12.31.
Found (%):	C, 73.61;	H, 9.17;	N, 12.18.

Example 89

Cis-1,3-bis[[3-(4-dimethylaminophenyl)-1-furfurylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 68-73°C (free form)
MS(FAB): m/e = 627 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1639(s), 1519(s)
NMR(DMSO-d_6) δ: 7.91 (2H, s, NH x 2), 7.55 (2H, m, Ar-H), 7.22 (4H, d, J = 9.2Hz, Ar-H), 6.64 (4H, d, J = 9.2Hz, Ar-H), 6.38 (2H, m, Ar-H), 6.28 (2H, m, Ar-H), 4.52 (4H, s, Ar-CH_2 x 2), 3.15 (4H, d, J = 5.5Hz, NCH_2 x 2), 2.82 (12H, s, $N(CH_3)_2$ x 2), 0.6-1.8 (10H, m)

Elemental analysis (for $C_{38}H_{46}N_6O_4 \cdot H_2O$)			
Calculated (%):	C, 67.06;	H, 7.50;	N, 13.03.
Found (%):	C, 66.91;	H, 7.21;	N, 12.82.

Example 90

Cis-1,2-bis[[3-(4-dimethylaminophenyl)-1-normalheptylureido]methyl]cyclohexane
The title compound was synthesized by the method in accordance with Example 1.
mp: 135-138°C (free form)
MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2923(brs), 1631(s), 1596(s), 1519(s)
NMR(DMSO-d_6) δ: 7.74 (2H, s, NH x 2), 7.19 (4H, d, J = 9.0Hz, Ar-H), 6.60 (4H, d, J = 9.0Hz, Ar-H), 3.2-3.4 (8H, m, NH_2 x 4), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.90 (2H, brs, CH x 2), 1.2-1.7 (28H, m), 0.85 (6H, t, J = 7.0Hz, CH_3 x 2)

Elemental analysis (for $C_{40}H_{68}N_6O_2 \cdot H_2O$)			
Calculated (%):	C, 70.55;	H, 10.06;	N, 12.34.
Found (%):	C, 70.38;	H, 10.26;	N, 12.00.

Example 91

Trans-1,2-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 108-114°C (free form)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2933(brs), 1629(s), 1616(s), 1519(s)
NMR(DMSO-d_6) δ: 7.77 (2H, s, NH x 2), 7.18 (4H, d, J = 8.8Hz, Ar-H), 6.62 (4H, d, J = 8.8Hz, Ar-H), 3.74 (2H, m, NCH x 2), 3.45 (2H, m, CH_2 x 2), 3.1-3.2 (2H, m, CH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.0-1.8 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2$)			
Calculated (%):	C, 72.34;	H, 9.27;	N, 13.32.
Found (%):	C, 72.08;	H, 9.50;	N, 13.10.

Example 92

Trans-1,2-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 125-129°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2920(s), 1646(s), 1629(s), 1556(s), 1517(s)
NMR(DMSO-d_6) δ: 8.39 (2H, s, NH x 2), 7.4-7.7 (8H, m, Ar-H), 3.1-3.8 (6H, m, NCH x 2, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.0-1.9 (34H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 61.13;	H, 8.98;	N, 10.69.
Found (%):	C, 61.24;	H, 8.80;	N, 10.41.

Example 93

Trans-1,2-bis[[3-(4-dimethylaminophenyl)-1-benzylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 109-113°C (free form)
MS(FAB): m/e = 647 (M^+_{+1})
IR(KBr) ν MAX: 2927(s), 1629(s), 1592(s), 1519(s)
NMR(DMSO-d_6) δ: 7.96 (2H, s, NH x 2), 7.1-7.4 (14H, m, Ar-H), 6.60 (4H, d, J = 9.1Hz, Ar-H), 4.54 (4H, s, NCH_2 x 2), 3.1-3.5 (4H, m, NCH_2 x 2), 2.81 (12H, s, $N(CH_3)_2$ x 2), 1.5-1.8 (6H, m), 1.0-1.2 (4H, m)

Elemental analysis (for $C_{40}H_{50}N_6O_2$)			
Calculated (%):	C, 74.27;	H, 7.79;	N, 12.99.
Found (%):	C, 74.10;	H, 8.05;	N, 12.70.

Example 94

Trans-1,2-bis[[3-(4-dimethylaminophenyl)-1-normalhexylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 112-117°C (dihydrochloric acid salt)

MS(FAB): m/e = 663 (M^++1)
IR(KBr) ν MAX: 2910(brs), 1652(s), 1517(s)
NMR(DMSO-d_6) δ: 8.40 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.0-3.6 (20H, NCH_2 x 4, $N(CH_3)_2$ x 2), 0.8-1.7 (36H, m)

Elemental analysis (for $C_{40}H_{66}N_6O_2 \cdot 2HCl \cdot 3H_2O$)			
Calculated (%):	C, 60.82;	H, 9.44;	N, 10.64.
Found (%):	C, 60.60;	H, 9.93;	N, 10.49.

Example 95

Cis-1,2-bis[[1-cyclohexylmethyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 102-106°C (free form)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2927(brs), 1631(s), 1590(s), 1521(s)
NMR(DMSO-d_6) δ: 7.75 (2H, s, NH x 2), 7.20 (4H, d, J = 8.8Hz, Ar-H), 6.61 (4H, J = 8.8Hz, Ar-H), 3.32 (4H, m, NCH_2 x 2), 3.13 (4H, m, NCH_2 x 2), 2.80 (12H, s, $N(CH_3)_2$ x 2), 0.8-2.2 (32H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2$)			
Calculated (%):	C, 72.91;	H, 9.48;	N, 12.75.
Found (%):	C, 72.87;	H, 9.83;	N, 12.53.

Example 96

Cis-1,2-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 149-154°C (dihydrochloric acid salt)
MS(FAB): m/e = 631 (M^++1)
IR(KBr) ν MAX: 2933(brs), 1646(s), 1556(s), 1540(s)
NMR(DMSO-d_6) δ: 8.47 (2H, s, NH x 2), 7.4-7.7 (8H, m, Ar-H), 3.73 (2H, m, NCH x 2), 3.2-3.5 (4H, m, NCH_2 x 2), 3.06 (12H, s, $N(CH_3)_2$ x 2), 1.0-1.9 (30H, m)

Elemental analysis (for $C_{38}H_{58}N_6O_2 \cdot 2HCl \cdot 2H_2O$)			
Calculated (%):	C, 61.69;	H, 8.72;	N, 11.36.
Found (%):	C, 61.79;	H, 8.90;	N, 11.10.

Example 97

Cis-1,2-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 1.
mp: 107-112°C (dihydrochloric acid salt)
MS(FAB): m/e = 659 (M^++1)
IR(KBr) ν MAX: 2921(brs), 1646(s), 1590(s), 1519(s)
NMR(DMSO-d_6) δ: 8.45 (2H, s, NH x 2), 7.5-7.7 (8H, m, Ar-H), 3.2-3.8 (6H, m, NCH x 2, NCH_2 x 2), 3.05 (12H, s, $N(CH_3)_2$ x 2), 1.0-2.0 (34H, m)

Elemental analysis (for $C_{40}H_{62}N_6O_2 \cdot 2HCl$)			
Calculated (%):	C, 65.64;	H, 8.81;	N, 11.48.
Found (%):	C, 66.02;	H, 8.43;	N, 11.42.

Example 98

Cis-1,2-bis[[3-(4-dimethylaminophenyl)-1-furfurylureido]methyl]cyclohexane

The title compound was synthesized by the method in accordance with Example 2.
mp: 106-110°C (dihydrochloric acid salt)
MS(FAB): m/e = 627 (M^++1)
IR(KBr) ν MAX: 2929(brs), 1656(s), 1646(s), 1517(s)
NMR(DMSO-d_6) δ: 8.43 (2H, s, NH x 2), 7.55 (2H, m, Ar-H), 7.2-7.5 (8H, m, Ar-H), 6.37 (2H, m, Ar-H), 6.30 (2H, d, J = 3.0Hz, Ar-H), 4.5-4.7 (4H, m, NCH_2 x 2), 3.2-3.5 (4H, m, NCH_2 x 2), 3.01 (12H, s, $N(CH_3)_2$ x 2), 1.93 (2H, brs, CH x 2), 1.2-1.7 (8H, m)

Elemental analysis (for $C_{36}H_{46}N_6O_4 \cdot 2HCl \cdot H_2O$)			
Calculated (%):	C, 60.24;	H, 7.02;	N, 11.71.
Found (%):	C, 60.10;	H, 7.30;	N, 11.55.

Pharmacological Test Examples

Compounds of the present invention were tested for their pharmacological effects by the following methods.

1) Inhibitory effect on ACAT (Acyl-CoA : cholesterol acyltransferase) enzyme (No.1)

Compounds of the invention were tested for their inhibitory effects on ACAT enzyme of rabbit liver microsome by the method of J.G. Heider (J. of Lipid Res., vol. 24, 1127-1134, 1983). More specifically, the test was done by measuring the amount of labelled cholesterol oleate ester produced from oleic acid CoA (coenzyme A) labelled by radiation. Table 1 shows the concentration of each test compound needed to inhibit 50% of the enzyme activity of the control group.

Table 9

Inhibitory effect on ACAT enzyme activity	
Example no. of test compound	IC_{50}(M)
7	10.0×10^{-8}
11	4.7×10^{-8}
15	3.8×10^{-8}
28	2.5×10^{-8}
42	6.0×10^{-8}
43	5.0×10^{-8}
61	3.6×10^{-8}
83	4.6×10^{-8}
YM-17E*)	2.3×10^{-8}

Note: *) a compound described in Example 47 of Japanese Unexamined Patent Publication No.117651/1990

2) Inhibitory effect on ACAT (Acyl-CoA : cholesterol acyltransferase) enzyme (No.2)

[2-1] ACAT enzyme activities of rabbit liver and small intestine mucosa microsomes

A white male rabbit was fed with a 1% cholesterol-containing food for four weeks and bleeding-slaughtered to extract its liver and small intestine. Microsomes of the liver and small intestine mucosa were prepared by the method of C. Marco et al. (Biochim. Biophys. Acta, 617, 458-471, 1980).

ACAT enzyme activities of the microsomes were determined by the method of J.G. Heider (J. Lipid Res., 24, 1127-1134, 1983). A test sample dissolved in 1% dimethylsulfoxide was added to a microsome fraction (100 µg), a phosphoric acid buffer (0.154 M) having pH 7.4, 1-^{14}C-oleoyl CoA (36 µM), dithiosleitol (2 mM) and bovine blood serum albumin (36 µg/ml). The reaction mixture adjusted to a final capacity of 0.5 ml was incubated at 37°C for 60 minutes. A mixture (6 ml) of chloroform and methanol (2:1) was added and the reaction was stopped. Cholesterol oleate was extracted with chloroform and separated by thin-layer chromatography. ACAT enzyme activities of the microsome fractions were determined by radiation measurement. Table 10 shows the results.

Table 10

Inhibitory effect on ACAT enzyme activity		
Example no. of test compound	IC_{50}(nM)	
	Liver of rabbit	Small intestine of rabbit
12	36	24
13	35	130
22	83	18
28	42	30
14-1	180	140
14-2	62	52
12-1	78	29
YM-17E*)	23	-

Note: *) a compound described in Example 47 of Japanese Unexamined Patent Publication No.117651/1990

[2-2] ACAT enzyme activities of human HepG2 and CaCo2 cells

Human HepG2 and CaCo2 cells purchased from ATCC (AMERICAN TYPE CULTURE COLLECTION) were used in this test.

Using RPMI 1640 medium for HepG2 and DMEM medium for CaCo2, HepG2 and CaCo2 cells were cultured with 40 ml of each medium containing 10% bovine blood serum, 50 I.U. of penicillin and 50 µg/ml of streptomycin in a 5% CO_2 incubator at 37°C. The cells were then monolayer-cultured with 80 ml of each medium containing 10 µg/ml of cholesterol and 5 µg/ml of 25-OH cholesterol in a 175 cm^2 flask for 5 hours. The homogenizes of these cells were subjected to centrifugation at 105,000 g to collect microsome fractions. ACAT enzyme activities of the microsome fractions were determined by the above-mentioned method. Table 11 shows the results.

Table 11

Inhibitory effect on ACAT enzyme activity		
Example No. of test compound	IC_{50}(nM)	
	Human HepG2	Human CaCo2
12	1.1	0.74
13	0.86	1.1
22	0.32	0.22
28	1.2	0.52
14-1	0.40	0.80
14-2	0.27	1.6
12-1	1.5	1.5
YM-17E*)	9.6	14

*) a compound described in Example 47 of Japanese Unexamined Patent Publication No.117651/1990

3) Cholesterol lowering effect

[3-1] Using a rat having high cholesterol, compounds of the invention were tested for their serum cholesterol lowering effects by the following method. A 6-week-old SD-type (Sprague-Dawley) male rat was fed with food containing 1% of cholesterol, 0.5% of cholic acid and 5% of olive oil for 2 days and then orally administered the food and a compound of the invention as dissolved in saline once a day for 5 days starting on day 3. Four hours after the final administration, a blood sample was taken. The total cholesterol in the serum of the test group was measured and compared with that of the control group. Table 2 shows what percentage of the cholesterol in the serum of the control group was reduced by means of the test compound.

Table 12

Cholesterol lowering effect		
Example no. of test compound	% 10 mg/kg	% 3 mg/kg
7	103	105
11	101	108
15	99	93
28	100	106
42	102	110
43	107	88
61	82	48
83	91	43
YM-17E*)	91	38

*) a compound described in Example 47 of Japanese Unexamined Patent Publication No.117651/1990

As clear from the above, the compounds of the present invention can inhibit ACAT enzyme activities of the experimental systems in vitro or in vivo.

[3-2] Using a rat having high cholesterol, compounds of the invention were tested for their serum cholesterol lowering effects by the following method. A 6-week-old SD-type (Sprague-Dawley) male rat was fed with food containing 1% of cholesterol, 0.5% of cholic acid and 5% of olive oil for 7 days. For the last 5 days, a test sample suspended in some drops of Tween 80 and saline was orally administered once a day. Four hours after the final administration, a blood sample was taken from celiac aorta of the rat under etherization. The total cholesterol in the serum of the test group was measured by the oxygen method and compared with that of the control group. Table 13 shows what percentage of the cholesterol of the serum of the control group was reduced by means of the test compound.

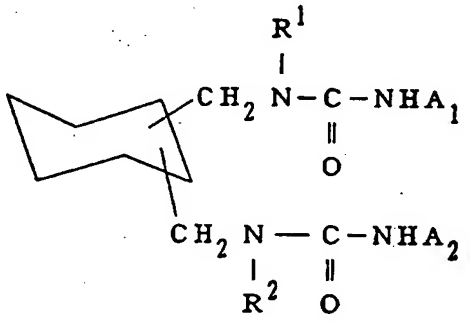
Table 13

Cholesterol lowering effect		
Example No. of test compound	% 3 mg/kg	% 1 mg/kg
12	92.6	96.2
13	96.2	76.8
22	97.2	77.6
28	106.5	70.2
14-1	96.2	80.9
14-4	98.8	79.9
12-1	108.3	100.4
YM-17E*)	38.0	-

*) a compound described in Example 47 of Japanese Unexamined Patent Publication No.117651/1990

Claims

1. A cyclohexanediurea derivative represented by the following formula (I):



(I)

wherein R^1 and R^2 are the same or different and they each represent a straight-chain or branched alkyl group having at least 3 carbons, a cycloalkyl group, a cycloalkyl group having a bridge head, a furyl group, a furyl lower alkyl group or an aralkyl group, A_1 and A_2 are the same or different and they each represent a phenyl, pyridyl, quinolyl, isoquinolyl or indolyl group which may have substituents; or a salt thereof.

2. A cyclohexanediurea derivative according to claim 1 wherein $R^1 = R^2$ and $A_1 = A_2$; or a salt thereof.

3. A cyclohexanediurea derivative according to claim 1 wherein the urea derivatives are linked to the cyclohexane ring by trans-1,4, cis-1,4 or cis-1,3 bond, R^1 and R^2 are the same or different and they each represent a cycloalkyl group or a branched alkyl group, and A_1 and A_2 represent 4-dimethylaminophenyl, 4-pyrrolidinophenyl or 4-piperidinophenyl; or a salt thereof.

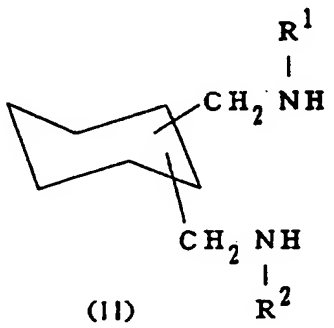
4. A cyclohexanediurea derivative according to claim 1 wherein R^1 and R^2 are the same or different and they each represent cyclopentyl, cyclohexyl, cyclobutyl or 4-methylcyclohexyl; or a salt thereof.

5. A cyclohexanediurea derivative according to claim 1 wherein A_1 and A_2 are the same or different and they each represent 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-pyrrolidinophenyl, 4-piperidinophenyl, or 4-morpholynophenyl; or a salt thereof.

6. A cyclohexanediurea derivative or a salt thereof which is one of the compounds or salts given below in (1)-(10):

(1) a trans-1,4-bis[[1-cyclopentyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(2) a trans-1,4-bis[[1-cyclohexyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(3) a trans-1,4-bis[[1-cyclohexyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(4) a trans-1,4-bis[[1-cyclohexyl-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane or a salt thereof;
(5) a trans-1,4-bis[[1-cyclohexyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane or a salt thereof;
(6) a trans-1,4-bis[[3-(4-dimethylaminophenyl)-1-(4-methylcyclohexyl)ureido]methyl]cyclohexane or a salt thereof;
(7) a trans-1,4-bis[[1-cycloheptyl-3-(4-dimethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(8) a trans-1,4-bis[[1-cycloheptyl-3-(4-diethylaminophenyl)ureido]methyl]cyclohexane or a salt thereof;
(9) a trans-1,4-bis[[1-cycloheptyl-3-(4-pyrrolidinophenyl)ureido]methyl]cyclohexane or a salt thereof; and
(10) a trans-1,4-bis[[1-cycloheptyl-3-(4-piperidinophenyl)ureido]methyl]cyclohexane.

7. A cyclohexanediurea derivative represented by the following formula (II):



(II)

wherein R^1 and R^2 are the same or different and they each represent a phenyl, pyridyl, quinolyl, isoquinolyl or indolyl group which may have substituents; or a salt thereof.

8. A cyclohexanediurea derivative according to claim 6 wherein $A^1 = A^2$; or a salt thereof.

9. An ACAT (Acyl-CoA : cholesterol acyltransferase) enzyme inhibitor containing an effective amount of the cyclohexanediurea derivative or its salt defined in claim 1 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition for hyperlipidemia which comprises an effective amount of the cyclohexanediurea derivative or its salt defined in claim 1 and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition for atherosclerosis which comprises an effective amount of the cyclohexanediurea derivative or its salt defined in claim 1 and a pharmaceutically acceptable carrier.

12. A method for inhibiting ACAT (Acyl-CoA : cholesterol acyltransferase) enzyme which comprises administering to a patient an effective amount of the cyclohexanediurea derivative or its salt defined in claim 1.

13. A method for treating hyperlipidemia which comprises administering to a patient an effective amount of the cyclohexanediurea derivative or its salt defined in claim 1.

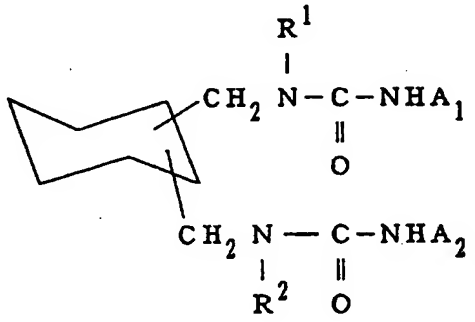
14. A method for treating atherosclerosis which comprises administering to a patient an effective amount of the cyclohexanediurea derivative or its salt defined in claim 1.

15. Use of the cyclohexanediurea derivative or its salt defined in claim 1 to inhibit ACAT (Acyl-CoA : cholesterol acyltransferase) enzyme.

16. Use of the cyclohexanediurea derivative or its salt defined in claim 1 to treat hyperlipidemia.

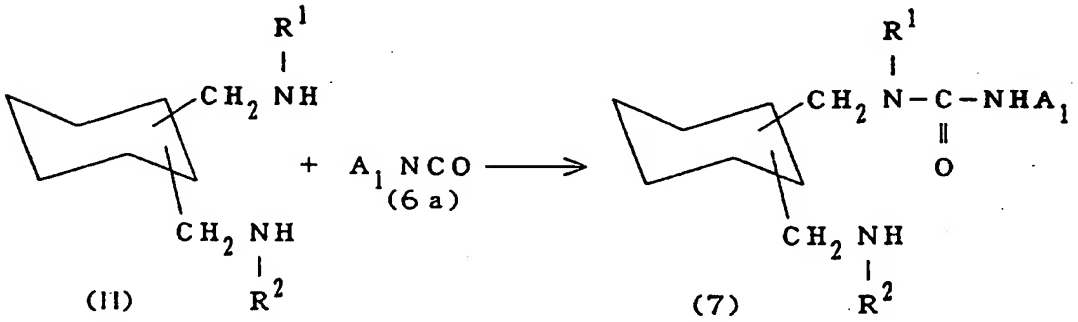
17. Use of the cyclohexanediurea derivative or its salt defined in claim 1 to treat atherosclerosis.

18. A method for producing a cyclohexanediurea derivative represented by the following formula (I):

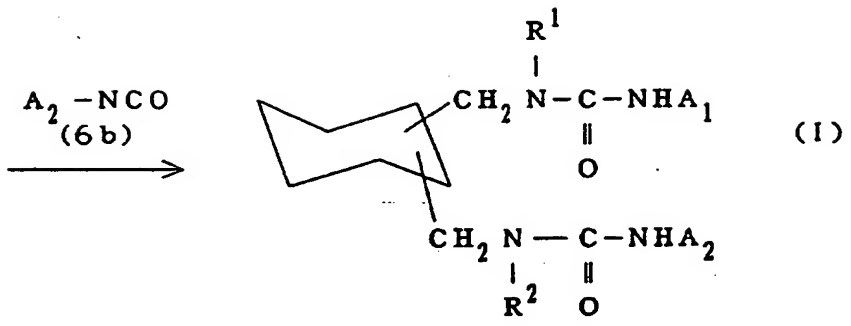


(I)

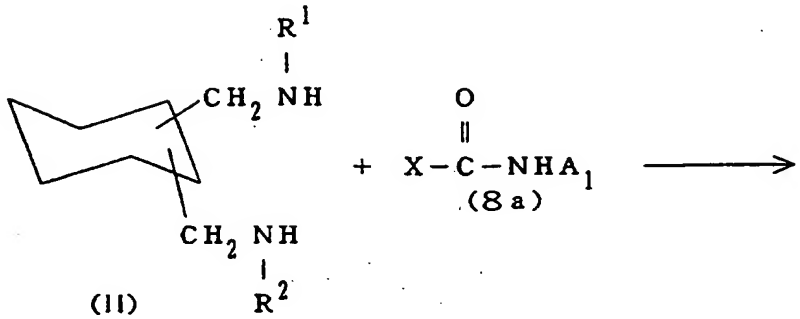
wherein R^1 and R^2 are the same or different and they each represent a straight-chain or branched alkyl group having at least 3 carbons, a cycloalkyl group, a cycloalkyl group having a bridge head, a furyl group, a furyl lower alkyl group or an aralkyl group, A_1 and A_2 are the same or different and they each represent a phenyl, pyridyl, quinolyl, isoquinolyl or indolyl group which may have substituents,
by one of the following processes A-D:
(Process A)

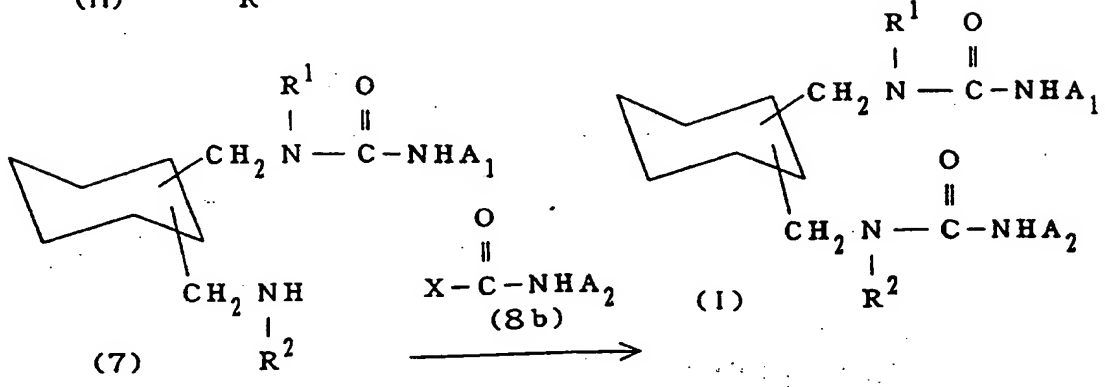


(II) (6a) (7)

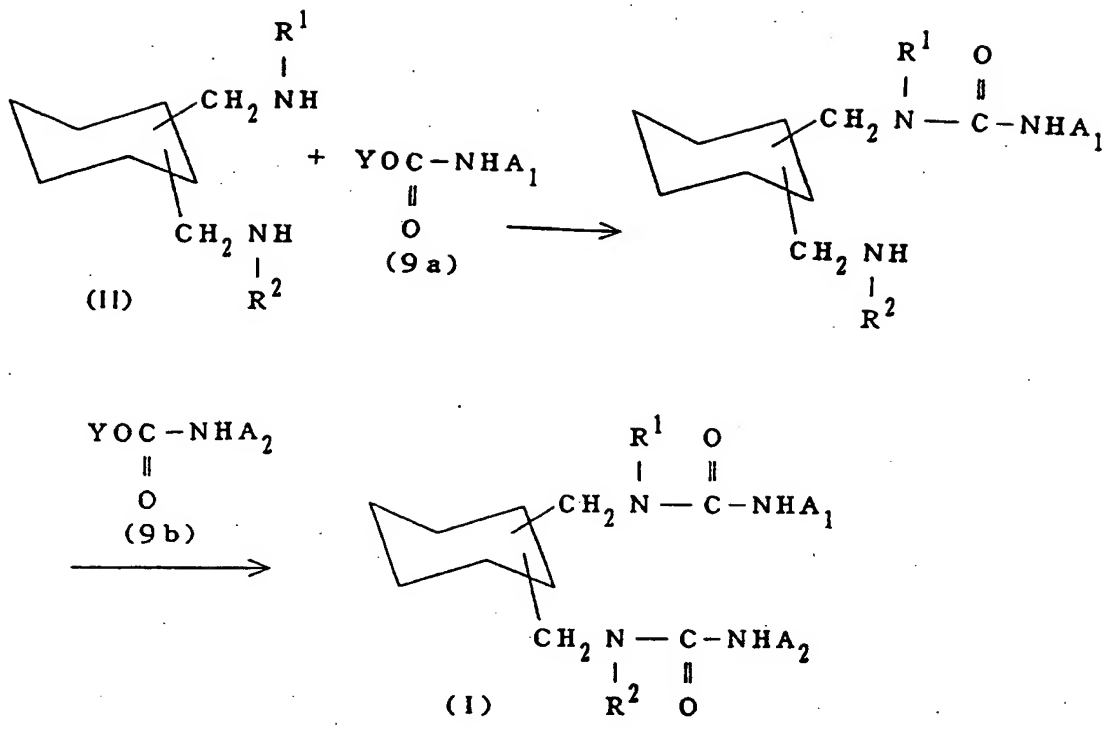


wherein R^1, R^2, A_1 and A_2 are as defined above,
(Process B)



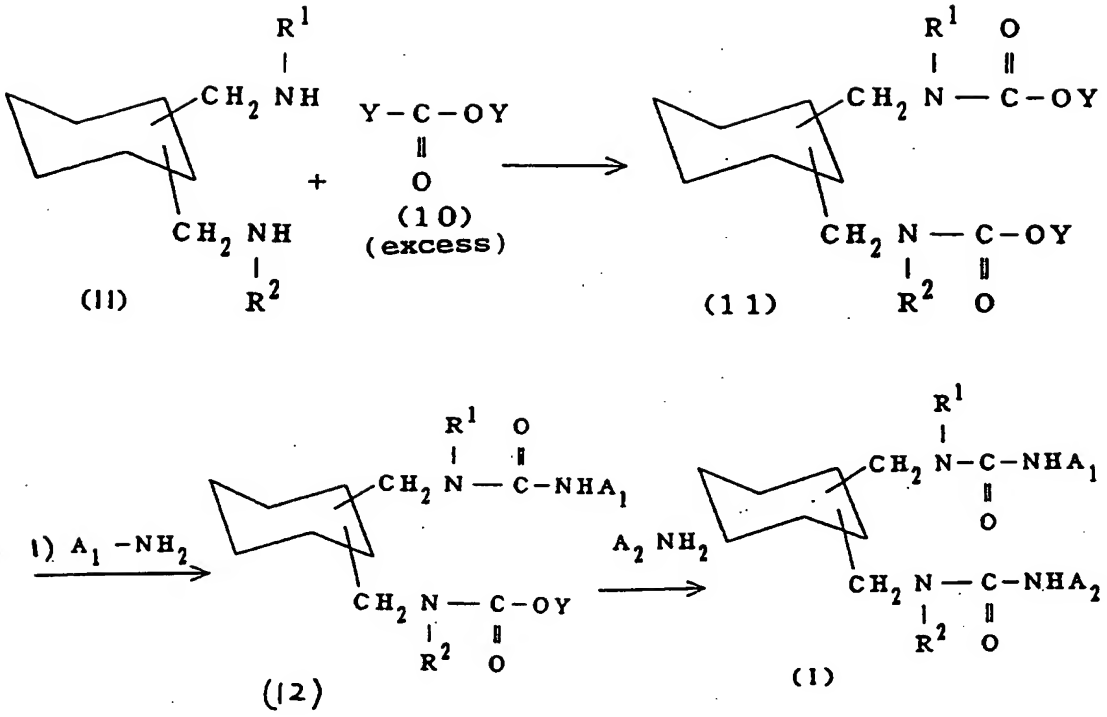


wherein R^1, R^2, A_1 and A_2 are as defined above,
(Process C)



wherein R^1 R^2, A_1 and A_2 are as defined above, and

(Process D)



wherein R^1, R^2, A_1 and A_2 are as defined above.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP94/01475

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl[6] C07C275/28, C07D213/72, 215/38, 217/22, 209/40, A61K31/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int. Cl[5] C07C275/26, 275/28, C07D213/72, 215/38, 217/22, 209/40, A61K31/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 2-117651 (Yamanouchi Pharmaceutical Co., Ltd.), May 2, 1990 (02. 05. 90), Pages 1 to 23 & US, A, 5,091,419 & US, A, 5,166,429 & US, A, 5,227,492 & EP, B1, 325,397	1-11, 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"E" earlier document but published on or after the international filing date
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
November 15, 1994 (15. 11. 94)	December 6, 1994 (06. 12. 94)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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